ONTarget

Resource Guide

Common Side Effects of Targeted Therapy

To Build Confidence and Skill in the Prevention and Management of Common Side Effects of Targeted Oncology Therapy

Care has been taken to ensure the accuracy of the information; however, it is not intended to provide a complete description of all side effects or to be used as a replacement for the product monographs of the targeted therapies that are discussed here. Since information on these new therapies is constantly evolving, it is advisable not to use this program as the sole source of information on this subject. You are encouraged to consult other sources of information as they become available.

The information in this document is provided solely as an educational service. Specific patient care decisions are the responsibility of the clinician who cares for the patient on a targeted therapy.

Medications

To view information about common side effects of a particular medication, click on the bookmarks in the left panel under Medication.

Alemtuzumab (MabCampath®)
Bevacizumab (Avastin®)
Cetuximab (Erbitux®)
Dasatinib (Sprycel®)
Erlotinib (Tarceva®)
Everolimus (Afinitor®)
Gefitinib (Iressa®)
Imatinib (Gleevec®) – CML
Imatinib (Gleevec®) – GIST
Lapatinib (Tykerb®)
Nilotinib (Tasigna®)
Panitumumab (Vectibix®)
Rituximab (Rituxan®)
Sorafenib (Nexavar®)
Sunitinib (Sutent®) – CML
Sunitinib (Sutent®) – GIST
Temsirolimus (Torisel®)
Trastuzumab (Herceptin®)

Overview of ONTarget

Introduction

Acknowledgements

The *Groupe* d'étude en oncologie du Québec (GEOQ) is a non-profit online organization dedicated to promoting communication and cooperation between professionals who are involved in the diagnosis, investigation, and research of treatments for different types of cancer and associated hematological conditions. The website **www.geoq.com** provides up-to-date oncology information to healthcare professionals in Quebec.

The scientific committee and expert review committee who developed this Resource Guide would like to thank GEOQ for hosting this program and providing expertise along the way during the design and development phase.

Why this Resource Guide was created

With an increase in the number of prescriptions for oral targeted therapy, **community pharmacists** need to be knowledgeable about the mechanisms of action, administration, basic pharmacokinetics, and common side effects of these anti-cancer medications. This Resource Guide is a practical tool for pharmacists to use in their day-to-day work.

Targeted therapies, which include monoclonal antibodies and small molecule inhibitors, have significantly changed the treatment of cancer over the past 10 years. These drugs are now a component of therapy for many common malignancies, including breast, colorectal, lung, and pancreatic cancers as well as lymphoma, leukemia, renal cell cancer, and multiple myeloma. The mechanisms of action and toxicities of targeted therapies differ from those of traditional cytotoxic chemotherapy.

While targeted therapies are generally better tolerated than traditional chemotherapy, they are associated with novel side effects, such as EGFR-induced acneiform rash and MKI-induced hand-and-foot syndrome. This Resource Guide presents practical strategies for the prevention and management of these common side effects for community pharmacists who see patients on targeted therapy in their daily practice.

What are targeted therapies

A number of new therapies in oncology target specific molecules that are involved in the development, growth, and progression of cancer in thriving human cells. Human cells receive and transmit vital information from their environment along biochemical signaling pathways. Cell surface receptors receive signals from the extracellular environment and transmit them into cells, activating a chain of signaling molecules, often called second messengers, which are aligned along specific pathways to the cell nucleus. These signals influence cellular:

- Growth
- Differentiation
- Reproduction
- Survival

A signaling pathway is triggered when a ligand binds to the extracellular portion of cell surface receptors. The ligand may be a growth factor, hormone, antibody, or other biochemical. The ligand activates the receptor, leading to signal transduction within the cell. Signaling molecules then transmit messages to a chain or pathway of other signaling molecules to the nucleus.

How targeted therapies work

Targeted therapies in oncology attack molecular targets on cell signaling pathways. The most typical targets are:

- Ligands that bind to and activate cell surface receptors
- Cell surface receptors
- Intracellular signaling molecules
- Transcription factors in the nucleus

Monoclonal antibodies generally work outside the cell. They target ligands that bind to cell surface receptors or the extracellular portion of cell surface receptors. Small molecule drugs generally work inside the cell. They target the intracellular portion of cell surface receptors, signaling molecules that relay messages through the cell or transcription factors within the cell nucleus.

The molecular targets of newer biologic therapies have been implicated in the development and progression of cancer. Many are overabundant, dysregulated, or abnormal in cancer cells. By targeting these molecules, newer therapies attack the mechanisms that lead to tumour formation and progression. However, they may also impact molecular targets in normal cells, leading to novel side effects.

Common side-effect profiles

The common side-effect profiles of these agents differ from those of traditional chemotherapeutic agents and hormonal agents. However, these common side effects are often predictable, based on the specific mechanism of action and molecular target of each agent.

Early identification of common side effects and timely intervention may ameliorate some common side effects and encourage patient adherence to targeted therapy, which may improve patient survival and quality of life.

This teaching program presents the common side effects of these agents and has compiled strategies for their prevention and management at the pharmacist level.

About this Resource Guide

Target audience and purpose

OnTarget was created primarily for **community pharmacists** but may also benefit hospital pharmacists in the:

- Appropriate prevention and management of common side effects that are associated with targeted cancer therapies
- Identification of key molecular targets that are blocked by targeted therapies in clinical use and may be targeted in future by newer agents
- Maintenance of patients on therapy and improvement of patient response and outcomes

Focus of Resource Guide

At the outset, the scientific committee made a number of critical decisions about the type of information and degree of detail that would be most practical and suitable for the target audience.

To this end, OnTarget focuses on the **prevention and management of common side effects**. The Resource Guide excludes:

- Information that is not typical or relevant to the daily practice of community pharmacists, e.g. dosage adjustment
- Information that can be accessed in detail in a product monograph, e.g., detailed pharmacokinetics, clinical trial data, manufacturers' definitions of common and very common side effects
- Information that is inconsistent in the product monographs and medical literature, e.g. frequency of occurrence (%) of common side effects
- Information that is updated regularly and is typically accessed by pharmacists on designated websites, e.g., up-to-date reporting of drug interactions
- Information dealing with infusion reactions, which occur with intravenous (IV) agents, as they are encountered in the clinic or hospital setting

The definition of "common" and "very common" side effects is based on reports in individual product monographs. Community pharmacists should be aware that manufacturers define these terms differently and consult the product monographs for more information.

Care has been taken to ensure the accuracy of the information; however, it is not intended to provide a complete description of all side effects or to be used as a replacement for the product monographs of the targeted therapies that are discussed here. Since information on these new therapies is constantly evolving, it is advisable not to use this program as the sole source of information on this subject. You are encouraged to consult other sources of information as they become available. The information in this document is provided solely as an educational service. Specific patient care decisions are the responsibility of the clinician who cares for the patient on a targeted therapy.

Evidence-based guidelines

There are no evidence-based guidelines on how to manage the common side effects that targeted therapies may induce in patients with cancer. The recommendations presented here are based on a review of the medical literature, expert opinion, and best clinical practices in oncology.

- Note: For complete description of all side effects of these agents, *please consult the product monographs.*

Organization of Resource Guide

The content in this Resource Guide is organized into eight chapters; each focuses on one particular therapy that is used to block a specific molecular target in patients with cancer. Each chapter discusses the following information:

- The official indication for each therapy
- A review of each therapy and the specific molecular target
- How each agent in the therapeutic group is administered
- The mechanism of action
- Basic pharmacokinetics
- Prevention and management of common side effects
- List of references

Chapters

- **Overview of ONTarget**
- **Overview of Anti-CD monoclonal antibodies**:
  Rituxumab (Rituxan®); Alemtuzumab (MabCampath®)
- **Overview of Bcr-Abl inhibitors**:
  Imatinib (Gleevec®); Dasatinib (Sprycel®); Nilotinib (Tasigna®)
- **Overview of c-Kit inhibitors**:
  Imatinib (Gleevec®); Sunitinib (Sutent®)
- **Overview of EGFR inhibitors**:
  Erlotinib (Tarceva®); Gefitinib (Iressa®); Cetuximab (Erbitux®); Panitumumab (Vectibix®)
- **Overview of HER2 inhibitors**:
  Lapatinib (Tykerb®); Trastuzumab (Herceptin®)
- **Overview of Multi-targeted kinase inhibitors (MKIs)**:
  Sorafenib (Nexavar®); Sunitinib (Sutent®)
- **Overview of mTOR inhibitors**:
  Everolimus (Afinitor®); Temsirolimus (Torisel®)
- **Overview of VEGF inhibitors**:
  Bevacizumab (Avastin®)
- **Quiz**
- **Program Evaluation**

Continuing Education

Goal and objectives

The goal of this Resource Guide is to help **community pharmacists** confidently assess and manage the common side effects that targeted cancer therapies may induce in patients with cancer.

Upon completion of this program, you will be able to:

- Identify the key molecular targets of medications in clinical use and under development
- Identify the common side effects of targeted cancer therapies, based on their specific target, and the common side effects of individual therapies
- Apply the most appropriate preventive strategies to minimize common side effects
- Educate and inform your patients about potentially common side effects
- Assess symptoms and apply the most appropriate management strategies to minimize impact on the patient's quality of life
- Contribute to patient adherence, thereby helping to improve treatment response and outcomes
- Make appropriate referrals to oncologists or other healthcare professionals, when required

Continuing education credits (CEUs)

The Canadian Council on Continuing Education in Pharmacy has awarded this program 10 CEUs. To obtain credits, you will need to complete a final quiz and a program evaluation. Once you have successfully completed the program, you will receive your certificate of participation by email. Accreditation of this program will be recognized by CCCEP under the file number # 1046-2009-346-I-P until August 19, 2012.

Final quiz and evaluation

In order to be eligible for continuing education credits, you must complete the final quiz with a minimum grade of 70% and complete the program evaluation. Please note that you are permitted only two attempts at the final quiz. This final quiz is comprised of 27 multiple-choice questions and requires approximately 30 minutes complete.

Instructions pertaining to quiz and evaluation

Once you have completed the entire program, print the quiz and the evaluation. You can access both by clicking on the bookmark ICON (left column) and then scroll down the table of contents. The quiz and evaluation can be found at the end of the program. Complete the quiz questions and the evaluation questions.

Fax your completed quiz and evaluation to fax number: 306-545-7795. Once you have successfully completed the program, you will receive your certificate of participation by email.

Note: The certificates will be emailed to you by CCCEP. They are sometimes filtered as "junk mail". Please check your "junk mail". If you have not received your certificate by email within 5 working days upon completing the quiz and program evaluation, please contact us: ***info@cccep.ca****.*
For any difficulties, call: 306-545-7790.

Who created this Resource Guide

A committee of practicing oncology pharmacists, experienced in hospital and community pharmacy practice, in conjunction with an expert review panel and in collaboration with the Groupe d'étude en oncologie du Québec, developed this Resource Guide.

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This program has been endorsed by the Groupe d'étude en oncologie du Québec (GEOQ), 2009 and the Canadian Association of Pharmacy in Oncology (CAPhO), 2009.

Disclosure of potential conflict of interest

This educational initiative was funded by an unrestricted educational grant from the following pharmaceutical companies: Hoffman-La Roche Ltd., Novartis Pharmaceuticals Canada Inc., and Pfizer Canada Inc. Industry involvement included the funding of honoraria for the independent oncology pharmacist scientific committee and expert reviewers, who received honoraria in recognition of their time and expertise in the subject matter.

To obtain copies of this Resource Guide

This Resource Guide is available in English and in French and for copies of the program in PDF format, free of charge, contact Lucie Surprenant, committee Chair. Lucie will provide you with electronic copies to host on your website. Email: **lucie.surprenant@ssss.gouv.qc.ca**.

Overview of Anti-CD monoclonal antibodies

This chapter contains information on the prevention and management of common side effects of some anti-CD monoclonal antibodies (MoAbs) that you are likely to encounter among cancer patients in your practice.

Anti-CD MoAbs

Rituximab (Rituxan®)
Alemtuzumab (MabCampath®)

There are no evidence-based guidelines on how to manage anti-CD MoAb-induced side effects. The recommendations presented here are based on a review of expert opinion and best practices in oncology. For a complete description of all side effects of these agents, please consult the product monographs.[1-2] Infusion reactions, which occur with intravenous (IV) agents, are usually encountered in the clinic or hospital setting and will not be described here.

Two medications are commonly used to inhibit the action of some CD antigens. Rituximab and alemtuzumab are intravenous medications with different molecular targets.[1,2]

CDs in cancer

Cancer cells survive by failing to undergo programmed cell death (apoptosis). They resist death by neutralizing the proteins within cells that control this natural process.[3] But there is more than one way for a cancer cell to die. MoAbs induce cell death by targeting cancer cells for destruction by the body's immune system.[1,4]

Anti-CD MoAbs use the same method to fight cancer as the body's natural antibodies. They target specific proteins (antigens) on cancer-cell surfaces. They bind to these antigens, marking the cells. The immune system can then identify the marked cells and kill them.[4]

One such antigen is CD-20, which is located on the surface of normal and malignant B-lymphocytes.[5] Another target is CD-52, an antigen on the surface of both T- and B-lymphocytes. CD-52 is also found on other immune-system cells – monocytes, macrophages, natural killer cells, and granulocytes.[4-7]

Because MoAbs bind to all cell surfaces with the specific antigen, they can destroy both abnormal and normal cells. The depletion of normal cells can lead to treatment-related side effects.[4-7]

Drug administration

Rituximab

- This medication is administered by intravenous infusion in the hospital or clinic setting.

Alemtuzumab

- This medication may be administered intravenously in the hospital or clinic setting[1-3]

Because these MoAbs are associated with hypersensitivity reactions and infusion-related toxicity, the rate of intravenous infusion of both drugs is gradually stepped up and patients are watched carefully during infusions.[1,2] When injected subcutaneously, the dosage of alemtuzumab does not require stepping up.[3] However, this mode of administration is not currently approved for use in Canada.

Prophylaxis

Patients on alemtuzumab may receive prophylaxis, such as trimethoprim/ sulfamethoxazole and famciclovir or acyclovir, during treatment to minimize the risk of serious opportunistic infections.[2]

Mechanism of action

Anti-CD MoAbs kill cancer cells directly by flagging them for destruction by immune cells and by recruiting complement factors to do the job.[1-3,7]

Rituximab

- This medication targets the CD-20 antigen, a protein on the surface of leukemia and lymphoma cells (B-lymphocytes). The MoAB binds to any CD-20 antigen that it finds – whether cells are normal or abnormal – marking them for death. The immune system then kills the cells in the same way that it kills invading bacteria or viruses. The body naturally produces new, healthy B cells in a few months.[1,7]

Alemtuzumab

- This medication targets CD-52 antigen on B- and T-lymphocytes, monocytes, macrophages, natural killer cells, and granulocytes. It kills cancer cells by:[2-7]
  - Delivering a surrogate signal to cells that triggers apoptosis
  - Targeting cells for destruction by immune cells
  - Recruiting complement factors to kill cells

Basic pharmacokinetics

There are no drug-interaction studies for either medication.[1,2] Alemtuzumab and rituximab may affect the body's ability to respond to live viral vaccines.[2,8] Patients are usually advised to update their vaccines before therapy begins. Live vaccines for measles, mumps, rubella, yellow fever, and meningitis may be detrimental in these immunocompromised patients.[8] Annual flu vaccination is recommended.[1,2]

Prevention and management of common side effects

The following table summarizes the common side effects of rituximab and alemtuzumab.[1,2] Infusion reactions are the most common adverse events.[1,2,5] The incidence of side effects varies from one medication to another. For example, skin rash occurs in 40% of patients treated with alemtuzumab but in only 15% of those who receive rituximab.[5]

Alemtuzumab is generally more toxic to the blood and immune systems than rituximab, because the CD-52 antigen is more common on immune-cell surfaces.[6] Alemtuzumab suppresses T cells, and it is associated with opportunistic infections. Patients are usually given preventive therapy and closely monitored for signs of infection.[9] Common side effects to alemtuzumab usually occur in the first week after therapy begins. Most are generally mild to moderate and tend to improve or resolve as treatment progresses.[2]

Rituximab does not target T-cells, so it rarely causes opportunistic infections.[1] To prevent low blood pressure (BP) during an infusion, patients taking rituximab are instructed not to take their BP pills for 12 hours before an infusion and to resume taking their pills after the infusion is completed.[2]

Common side effects of anti-CD monoclonal antibodies

Click on side effects highlighted in blue for more information and click on the arrow to return.

Rituximab[1,5]

Blood disorders
- Neutropenia, thrombocytopenia, anemia

Cardiovascular disorders
- Changes in blood pressure
- Fast heart rate
- Fluid retention (edema)
- Flushing

Eye disorders
- Watery or itchy eyes

Gastrointestinal disorders
- Anorexia
- Diarrhea
- Indigestion, cramps
- Nausea and vomiting

General disorders
- Asthenia/fatigue
- Dizziness
- Headache
- Pain (muscle, back, abdominal, joint)
- Rigors

Infection

Infusion reactions
- Chills, fever

Respiratory disorders
- Bronchospasm
- Cough
- Dyspnea
- Runny nose, sinusitis
- Throat irritation

Skin disorders
- Rash, pruritis

Alemtuzumab[2,5]

Blood disorders
- Neutropenia, thrombocytopenia, anemia

Infusion reactions
- Chills, fever

Infection
- Opportunistic infections

General disorders
- Asthenia/fatigue
- Dizziness
- Headache
- Insomnia
- Pain (muscle, back, abdominal, joint)
- Rigors
- Sepsis

Respiratory disorders
- Bronchospasm
- Cough
- Dyspnea
- Runny nose, sinusitis
- Throat irritation

Cardiovascular disorders
- Changes in blood pressure
- Fast heart rate
- Fluid retention (edema)

Gastrointestinal disorders
- Anorexia
- Constipation
- Diarrhea
- Indigestion, cramps
- Nausea and vomiting
- Stomatitis

Skin disorders
- Rash, pruritis

Eye disorders
- Watery or itchy eyes

Opportunistic infection

Alemtuzumab decreases the body's ability to respond to infection. It may cause severe infections and opportunistic infections, such as *pneumocystis carinii* pneumonia (PCP) and herpes virus infections. It can reactivate CMV, Epstein-Barr virus, and hepatitis in patients with a history of infection.[2,3] These infections are not always eliminated by preventive therapy.[2,3]

Life-threatening skin reaction

Although rash is a common side effect of rituximab, severe skin reactions can be life-threatening. Refer any patient who has a severe rash with blistering for emergency care.[1]

Infection

Patients on anti-CD MoAb therapy have a weaker immune system due to cancer. The incidence of infection varies, depending on the type of treatment, patient's disease status, co-existing medical conditions, number of treatments, and history of prior infection.[9]

Prevention

Physicians, nurses and pharmacists educate patients to recognize the symptoms of common infections, including:[1,2]

- Bacterial infections
- Colds
- Fungal infections
- Urinary tract infections
- Viral infections, such as shingles, Epstein-Barr, hepatitis, and herpes virus
- Yeast infections

Refer any patient with signs of infections to a doctor for immediate care.[1,2]

Prescribed therapy (alemtuzumab)

- Antibacterial therapy to prevent PCP and antiviral therapy begins at the start of therapy and continues for a minimum of 2 months after the last dose or until CD4+ counts are ≥200 cells/μL to prevent viral reactivation[9]
- Antifungal prophylaxis is not routinely recommended[8]

Key facts: Infection

Anti-CD MoAbs also target normal, healthy immune cells, compromising the body's response to infection.[5,9] The severity of anti-CD MoAb-induced infections ranges from mild to life-threatening.[1,2] Careful monitoring and management of infections are essential to enable patients to fully benefit from these therapies and improve their chances of survival.[9]

Advise patients with general signs of infection to seek medical care:[4,7]

- Aching muscles
- Cough
- Feeling cold or shivery
- Fever
- Headaches
- Pain when passing urine
- Sore throat

Alemtuzumab, in particular, may reactivate dormant viruses, such as herpes virus, cytomegalovirus (CMV), hepatitis, and Epstein Barr virus, and open the door to opportunistic infections, such as Pneumocystis carinii pneumonia (PCP), in immunocompromised patients.[9]

Common side effects of alemtuzumab include bacterial, fungal, viral, and protozoan infections.[2]

- Bacterial infections may appear during the first weeks of therapy and happen less often as treatment continues.[9]
- Fungal infections often occur soon after therapy ends.[9]
- Viral infection, particularly CMV reactivation, typically occurs between the third and eighth weeks of therapy then gradually tapers off.[9]

Rarely, hepatitis B infections may occur in patients taking rituximab. Encourage patients with the following symptoms to contact their doctor for evaluation and treatment:[1]

- Abdominal pain
- Feeling sick
- Joint pain
- Loss of appetite
- Tiredness
- Yellowing of skin or eyes (jaundice)

References

1. Rituximab product monograph. Hoffman-LaRoche Ltd., February 18, 2009.
2. Alemtuzumab product monograph. Genzyme Corporation. January 27, 2009.
3. Gribben JG, Halleck M. Rediscovering alemtuzumab: current and emerging therapeutic roles. Br J Haematol 2009;144:818-831.
4. Cancer Research UK. Alemtuzumab. Cancer Help. November 2007. Accessed at: www.cancerhelp.org.uk/help/default.asp?page=29354.
5. Dillman RO, Hendrix CS. Unique aspects of supportive care using monoclonal antibodies in cancer treatment. Support Cancer Ther 2003;1:38-48.
6. Christian BA, Lin TS. Antibody therapy for CLL. Semin Hematol 2008;45:95-103.
7. Cancer Research UK. Rituximab. Cancer Help. November 2007. Accessed at: www.cancerhelp.org.uk/help/default.asp?page=29372.
8. Sehn L. Follicular lymphoma: monitoring patients on rituximab maintenance therapy. New Evidence in Oncology 2008;7(July):26-29.
9. Elter T, Vehreschild JJ, Gribeen J, Cornely OA, et al. Management of infections in patients with chronic lymphocytic leukemia treated with alemtuzumab. Ann Hematol 2009;88:121-132.

Overview of BCR-ABL inhibitors

This chapter contains information on the prevention and management of common side effects of Bcr-Abl inhibitors that you are likely to encounter among cancer patients in your practice.

There are no evidence-based guidelines on how to manage the common side effects of Bcr-Abl inhibitors. The recommendations presented here are based on a review of expert opinion and best practices in oncology. For a complete description of all side effects of these agents, please consult the product monographs.[1-4]

Bcr-Abl inhibitors

Imatinib (Gleevec®)
Dasatinib (Sprycel®)
Nilotinib (Tasigna®)

Three oral medications are available that inhibit the action of the Bcr-Abl tyrosine kinase.[1-4] Their mechanisms of action and side effects are similar.[1-4,5]

While these agents may inhibit other tyrosine kinases, the focus of this chapter is Bcr-Abl inhibition and the side effects that occur in patients who are treated for chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL).

Bcr-Abl in cancer

The primary target of Bcr-Abl inhibitors is the Bcr-Abl, an oncoprotein that is produced by the Philadelphia (Ph) chromosome, a mutated strand of DNA. This chromosome is created when small sections of DNA from chromosomes 9 and 22 switch places, a process known as translocation.[4-6]

The oncoprotein Bcr-Abl is believed to cause chronic myeloid leukemia (CML). More than 90% of adults with CML and up to 30% of adults with ALL have the abnormal Philadelphia chromosome (Ph+).[6]

Bcr-Abl inhibitors target a tyrosine kinase (TK) on the Abl portion of the oncogene. TKs are essential for normal cell signaling. Inside cells, these enzymes regulate:[4]

- Differentiation
- Function
- Motility
- Proliferation
- Survival

The Bcr-Abl TK activates other signaling proteins within the cell. These proteins in turn trigger other signaling proteins, leading to an expanding cascade of protein activation. The continuous transmission of signals triggers uncontrolled cell growth.[5]

The Bcr-Abl TK uses a phospate from ATP, a free-floating biochemical that has a binding site on Bcr-Abl, to activate other signaling proteins. If the ATP binding site is occupied, ATP cannot donate the phosphate and Bcr-Abl cannot activate the signaling proteins that promote cell growth. Bcr-Abl inhibitors target this binding site to inactivate Bcr-Abl tyrosine kinase and prevent the progression of leukemia.[5]

Drug administration

The dosing schedule for these medications depends on disease and stage. Dosing modification is common, based on patient response, side effects, and concurrent therapy.[6] Treatment interruptions and non-adherence to imatinib may lead to undesirable clinical outcomes, including a suboptimal therapeutic response.[12]

How to take Bcr-Abl inhibitors

- Take imatinib with food to avoid nausea and vomiting.[5]
- Take antacids containing aluminum hydroxide or magnesium hydroxide up to 2 hours before or 2 hours after dasatinib.[2]
- Nilotinib must be taken on an empty stomach, as food increases its absorption.[3,8]
- Use caution when taking acetaminophen (e.g., Tylenol®) with imatinib, because of an increased risk of hepatoxicity.
- Avoid grapefruit, grapefruit juice, star fruit, pomegranate juice, and Seville oranges.[1]
- Long-term suppression of gastric acid with stomach ulcer medications reduces systemic exposure to dasatinib.[2,6]

Imatinib

- Advise patients to take imatinib during a meal with a glass of water, once or twice daily, depending on dosage. Patients unable to swallow the tablets can drop them into a glass of water or apple juice, stir until they are disintegrated, and drink immediately. Leftover traces must be consumed.[1]

Dasatinib

- This medication is taken once daily – with or without food. Unlike imatinib, the tablets must be swallowed whole. They cannot be cut or crushed.[2]

Nilotinib

- There are very strict requirements for taking nilotinib. Doses are taken twice daily at 12-hour intervals. Capsules are swallowed whole with a glass of water. Patients cannot eat for at least 2 hours before and at least 1 hour after taking nilotinib.[3]

Patients who miss a dose of Bcr-Abl inhibitor should take their next dose as scheduled. They should not take a double dose to make up for the forgotten dose.

Mechanism of action

Imatinib

- This medication inhibits the TK on Bcr-Abl. It fills the ATP-binding pocket of Bcr-Abl, neutralizing TK activity. Through this mechanism of action, imatinib:[1,4]
  - o inhibits cell growth and proliferation
  - o induces cell death

Skin or hair colour changes

Imatinib
A small percentage of patients on imatinib may experience a repigmentation of grey hair.[18]

Dasatinib

- This medication inhibits the Bcr-Abl TK, along with the src family of kinases and TKs on receptors for c-Kit, ephrin, and PDGF-beta.[2,6] It may use these alternate signaling pathways to overcome imatinib resistance.[6] This second-generation TK inhibitor differs structurally from imatinib.

Nilotinib

- This medication is a second-generation TK inhibitor of Brc-Abl, Kit, PDGFR and ephrin receptor kinase.[3,6] It disrupts enzymatic activity by adhering to the ATP-binding pocket of the Bcr-Abl TK. Nilotinib is structurally related to imatinib.[6]

Basic pharmacokinetics

Bcr-Abl inhibitors are metabolized via the cytochrome P450 isoenzyme CYP3A4 system in the liver.[1-3,6] Drugs that are known to induce CYP3A4/5 may decrease plasma concentrations of imatinib, reducing the efficacy of the treatment If these medications cannot be avoided, strict monitoring for efficacy or toxicity is recommended in patients taking Bcr-Abl inhibitors.[6]

Nilotinib also inhibits CYP3A4, 2C8, 2C9, 2D6, and UGT1A1, increasing the serum levels of medications that are metabolized by these enzymes.[6] In addition, it induces CYP2B6, 2C8, and 2C9, reducing the serum levels of medications that are eliminated by these pathways.[6]

Prevention and Management of Common Side Effects

Bcr-Abl inhibitors are generally well tolerated[1-3] and most side effects resolve after dosage reduction or drug holiday.[6]

The side-effect profiles of these medications are similar but differ in some ways. For example, fluid retention, which usually manifests as periorbital edema, is a common side effect of imatinib (62% to 72% of patients) and dasatinib (50% of patients) but not nilotinib (0%).[6,8] Common side effects of each medication appear in the following table.[1-3,6]

The most common side effect of Brc-Abl inhibitors is myelosuppression – the suppression of bone marrow activity, which results in low blood cell counts.[1-3,8] Signs and symptoms include fatigue, weakness, spontaneous bleeding or bruising, and frequent infections with fever, chills, sore throat or stomatitis. Refer any patient who exhibits this constellation of symptoms to an oncologist for immediate evaluation.

For example, severe, dose-limiting side effects occur in only 2% to 5% of patients taking imatinib.[13]

Very common and common side effects of Bcr-Abl inhibitors

Click on side effects highlighted in blue for more information and click on the arrow to return.

Imatinib

Very common

Cardiovascular disorders
- **Fluid retention**, e.g., swelling around eyes, weight gain

Gastrointestinal disorders
- Abdominal pain, **diarrhea**, indigestion, nausea, vomiting,

General disorders
- **Bone, joint, and muscle pain**
- Fatigue
- Headache
- Muscle cramps
- Skin disorders
- **Rash**, pruritis

Common

Gastrointestinal disorders
- Abdominal swelling, constipation, gas, gastritis, heartburn, loss of appetite, mouth sores, taste disturbance, weight loss

General disorders
- Allergies, bleeding or bruising, chills, dizziness, hair loss, hot flushes, infections, insomnia, nose bleeds, night sweats, numbness, tingling, weakness

Eye disorders
- Blurred vision, conjunctivitis, dry eye, increased tears

Musculoskeletal disorders
- Joint swelling, muscle tension

Skin disorders
- Loss of skin sensitivity, sun sensitivity

Dasatinib

Common

Cardiovascular disorders
- Fluid retention

Gastrointestinal disorders
- **Diarrhea**, nausea, stomach pain, vomiting

General disorders
- Fatigue; fever; headache; **bone, joint, and muscle pain**, pain

Hematologic disorders
- Bleeding
- Infection

Respiratory disorders
- Cough, dyspnea, pleural effusion

Skin disorders
- Rash

Nilotinib

Very common

Gastrointestinal disorders
- **Diarrhea**, constipation, nausea, vomiting

General disorders
- Fatigue, headache

Skin disorders
- Pruritis, rash

Common

Gastrointestinal disorders
- Abdominal pain, gas, indigestion

General disorders
- **Bone, joint, and muscle pain**
- Dizziness, feeling unwell, hot flushes, insomnia; sensation of spinning; night sweats, hyperhidrosis; tingling or numbness; voice disorder

Skin disorders
- Hair loss, red or dry skin

Refer for medical attention: Imatinib

Tell patients with these common symptoms to consult their doctor:[1]

- Localised edema (swelling or pain in one part of the body)
- Low blood cell count (weakness; spontaneous bleeding or bruising; frequent infection with sore throat, chills, sore mouth or mouth ulcers)
- Peripheral edema (rapid weight gain, facial swelling or other signs of fluid retention)

Tell patients with these uncommon symptoms to see their doctor immediately:[1]

- Acute respiratory failure or pulmonary fibrosis (difficult or painful breathing, cough)
- Cellulitis (acute skin swelling)
- Cerebral edema, increased cranial pressure, stroke (severe headache, weakness or paralysis, seizures, difficulty speaking)
- Difficulty hearing
- Eye disorders (sudden change in eyesight or visual impairment)
- Gastrointestinal disorders (stomach pain, nausea, tarry dark stools or bloody urine)
- Heart disorders (crushing chest pain or irregular heartbeat)
- Hematologic disorders (bruising)
- Lightheadedness, dizziness or fainting
- Liver disorders (yellowing skin or eyes, light-coloured urine, loss of appetite, nausea)
- Potassium imbalance (muscle weakness, muscle spasms, abnormal heart rhythm)
- Raynaud's syndrome (cold or numb fingers or toes)
- Urinary tract infection (low urine output, thirstiness)

Tell patients with these rare side effects to seek emergency care:[1]

- Avascular necrosis or hip osteonecrosis (painful hips, difficulty walking)
- Inflammatory bowel disease (nausea, diarrhea, vomiting, abdominal pain, fever)
- Low red blood cells (pale skin, fatigue, breathlessness, dark urine)
- Serious skin disorders (severe rash, blistering or peeling skin, raised red or purple skin patches, itchy burning rash)

Refer for medical attention: Dasatinib

Refer patients with any of the following signs or symptoms to a doctor or emergency room immediately:[2]

- Bleeding disorders (hemorrhage; bleeding or bruising with an injury, no matter how mild)
- Cardiovascular disorders, such as congestive heart failure or pulmonary edema (dizziness, irregular or forceful heartbeat, or fainting)
- Low blood counts (fever, sore throat, weakness, bruising, frequent infections)
- Pleural or pericardial effusion (swelling, weight gain, increased shortness of breath, other signs of fluid around lungs or heart)
- Serious infection (fever, severe chills)

Refer for medical attention: Nilotinib

Advise patients with any signs or symptoms of the following side effects to see their doctor immediately:[3]

- Blood disorders (fever, sore throat, weakness, bruising, frequent infections)
- Eye disorders (Blurred or loss of vision, blood in eye)
- Fluid retention (swelling, weight gain, increased shortness of breath)
- Gastrointestinal disorders (abdominal pain, nausea, vomiting, black stools, constipation, swollen abdomen)
- Hyperglycemia (excessive thirst, high urine output, increased appetite with weight loss, fatigue)
- Kidney problems (Thirst, dry skin, dark urine, low urine output)
- Liver problems (yellow skin or eyes, loss of appetite, light-coloured urine, nausea)
- Skin disorders (rash, painful red lumps, joint or muscle pain)
- Advise patients with any signs or symptoms of the following side effects to seek emergency care immediately:[3]
- Blood clots (swelling and pain in one part of body)
- Lung disorders including pleural effusion or pulmonary edema (difficulty breathing, coughing, wheezing, swelling of hands and feet)
- QT interval prolongation or other heart problems, including chest pain, hypertension, irregular heartbeat, palpitations, fainting
- Serious infection, including pancreatitis (fever, severe chills)
- Stroke (weakness or paralysis, headache, difficulty speaking, delusions)

Diarrhea

Diarrhea is a very common side effect of Bcr-Abl inhibitors. It occurs in up to 45% of patients on dasatinib or imatinib and up to 22% of patients on nilotinib.[1-3] Dietary modifications are not recommended in anticipation of diarrhea.[21]

Prevention	No prevention measures are recommended.
Management OCT therapy[26] **Refer to doctor if moderate diarrhea does not improve after 24 hours of treatment**	Aggressive use of loperamide (e.g., Imodium®) for early-onset diarrhea **Mild to moderate (less than 4 loose stools per day)** • Follow instructions on package insert: 2 tablets immediately, then 1 tablet after each liquid bowel movement (maximum: 8 tablets/24 hours) **Moderate (more than 4 to 6 loose stools per day or night-time diarrhea)** • 2 tablets immediately, then 1 tablet every 2 hours during the day and 2 tablets every 4 hours during the night until bowel movements are normal for at least 12 hours • **This dosage is higher than packaging recommendations. Advise your patients that it is important to take the medication at higher doses to stop diarrhea**
Replace lost fluids[21,22,26]	• Fluid intake is more critical than food intake in patients with diarrhea. To replace lost fluid, advise patients with no contraindication to increase intake by up to 3 to 4 litres per day. • Drink several types of fluid, including plain water and electrolyte-containing drinks, such as clear broth, gelatin desserts, sports drinks, flat soft drinks, or decaffeinated tea
Anal care[21]	Advise patients to: • Clean the anal area with mild soap and warm water after each bowel movement to prevent irritation • Apply a barrier cream or ointment, such as petroleum jelly or Isle's paste • Soak in a warm bathtub or sitz bath to relieve discomfort • Examine the anal area for red, scaly or broken skin
Diet[22]	Advise patients to: • Advise patients to eat and drink small quantities of food often • Avoid spicy, greasy, or fried foods • Follow the BRAT (banana, rice, applesauce, toast) diet, along with clear liquids, until diarrhea begins to resolve • Avoid cabbage, Brussels spouts, and broccoli, which may produce stomach gas, bloating and cramps

Key facts: Diarrhea

Most cases of Bcr-Abl inhibitor-induced diarrhea are mild to moderate.[1-3,7-9] There are no clinical practice guidelines for the management of this side effect, but experts generally recommend the use of anti-diarrheal medications.[7,9,10]

When patients seek OTC treatment for diarrhea, it is important to ask them about:[19]

- Number of stools per day and stool composition, e.g., watery, presence of blood, nocturnal
- Presence of diarrhea before their last treatment
- Medication profile to identify other agents that may contribute to diarrhea
- Dietary profile
- Signs and symptoms of complicated diarrhea, including:
  - Blood in stool
  - Dehydration, e.g., oral dryness, low urine production or dark yellow urine, weight loss, dry eyes or mouth, sunken eyes, low pulse, dizziness or feeling faint when getting up
  - Fever
  - Lethargy or altered mental state
  - Nausea and vomiting
  - Signs of infection
  - Stomach cramps

Rash

Rash often but not always appears soon after the start of therapy. It occurs in about one-third of all patients taking imatinib but has a lower incidence of about 20% in patients on nilotinib and dasatinib.[1,8,9]

Prevention

A proactive approach is critical in managing rash. When patients begin therapy, advise them to:[15-17]

- Cleanse with mild soaps or cleaners or bath or shower oils to avoid skin dryness.
- Moisturize twice a day with a colloidal oatmeal lotion, such as Aveeno® lotion, or thick, emollient-based creams, such as Neutrogena® Norwegian Formula hand cream, or Vaseline Intensive Care® Advanced Healing Lotion.
- Use only fragrance- , alcohol-, and dye-free lotions and cosmetics.
- Use a dermatologist-approved cover-up, such as Dermablend® or Cover FX®, to conceal the rash.
- Remove make-up with a gentle, skin-friendly cleanser, e.g., Neutrogena®, Dove®
- Use a broad-spectrum sunscreen (SPF 15 or greater) that contains zinc oxide or titanium dioxide.
- Avoid hot showers or baths

Management

OTC therapy

Mild to moderate rash[9,11]

- Antihistamine (diphenhydramine)
- Topical steroid (hydrocortisone 0.5%)
- Coal tar preparations

Prescribed therapy

Moderate to severe[8,9,15]

- A short course of oral corticosteroids, with or without topical triamcinolone acetonide 0.1% ointment
- Temporary interruption of therapy until resolution of rash with a rechallenge at low dose

Key facts: Rash

Rash is more likely to occur in women and patients on higher doses.[9] In the most common rash, skin spots and bumps appear on the forearms, trunk, and, sometimes, the face. They are often itchy, and with scratching, may become infected and crusty. This generalized rash is usually mild, and most cases are self-limited – have a natural lifespan.[8]

Early recognition of rash symptoms, a prompt start of symptomatic therapy, and if necessary, withdrawal of the Bcr-Abl inhibitor are the mainstays of treatment.[9] Mild to moderate symptoms are managed while the patient remains on therapy.[9] Refer any patient with a severe rash to a doctor for evaluation and treatment.[5,7,9]

Rash may worsen after sun exposure.[8]

Unlike allergic rashes, Bcr-Abl inhibitor-induced rash may not recur when a medication is restarted at a lower dose after a temporary suspension of therapy.[7] Patients who develop a rash on imatinib do not appear to have a recurrence on dasatinib.[7]

Bone, joint, and muscle pain

About 25% to 50% of patients on imatinib,[9] 12% to 35% of patients on dasatinib,[2] and 6% to 8% of patients on nilotinib[3] develop aching bones or muscles or muscle cramps. Muscle and bone pain is usually mild to moderate and manageable without a reduction of imatinib therapy.[9]

Prevention	No preventive measures are recommended.
Management	The following measures may provide relief from muscle aches or cramps:[9,10] • Calcium supplements • Magnesium supplements • Mild pain medications (except acetaminophen with imatinib) For mild bone aches and pain:[10] • NSAIDs in patients with platelet counts of greater than 100,000/mm^3 and no history of GI bleeding

Key facts: Bone, joint, and muscle pain

Muscle cramps usually occur in the hands, feet, calves, or thighs of patients on Bcr-Abl inhibitors. The cramps have been described as sustained muscular contractions. The pattern, frequency, and severity of muscle cramps do not tend to change over time. Muscle cramps may be related to exertion or tend to happen at night.[9,10]

Patients on imatinib can take NSAIDs for muscle and bone pain – as long as their platelet count is normal.[5]

Bone and joint pain tends to begin in the first month of therapy and often abates after a few months. Pain usually afflicts the leg bones, hips, and knees and may appear in an asymmetrical pattern.[10]

There are no evidence-based guidelines for prevention or treatment, but anecdotal reports and expert experience have suggested that in some patients the use of mineral supplements may ease pain.[9-11]

Fluid retention

Fluid retention (edema) is a common side effect of imatinib and dasatinib but not nilotinib.[1-3] It develops in at least 50% of patients taking imatinib and from 10% to 22% of patients taking dasatinib.[7-10]

Prevention

Advise your patients to:[8-9]

- Limit salt intake

For swollen eyelids or swelling around eyes:[8]

- Elevate head during sleep

Management

OTC therapy

Mild periorbital fluid retention

- For swelling around eyes, elevate the head during sleep or use skin-tightening agents, e.g., topical Preparation H® containing phenylephrine or lanolin (avoid eye contact)[8]

Prescribed therapy

Mild peripheral fluid retention

- Topical eye ointments with phenylephrine 0.25%[8,9]
- Topical corticosteroid (e.g., hydrocortisone 1%)[9]

Moderate fluid retention

- Low-dose loop diuretic, e.g., furosemide with calcium and magnesium supplements[8]
- Close electrolyte monitoring[8]

Key facts: Fluid retention

Peripheral fluid retention

Peripheral fluid retention (edema) is usually superficial and mild to moderate in severity. Its occurrence is dose-related. The most frequent form of fluid retention is swollen eyelids or swelling around the eyes (periorbital edema), which is more pronounced in the morning and often associated with swelling of ankles, feet and lower legs.

Peripheral fluid retention tends to improve over time.[8] It occurs more frequently in:[10]

- Women
- Adults over 65 years of age
- Patients with a history of heart or kidney problems

Pleural effusion

Pleural effusion (excess fluid around the lungs) is rare in patients taking imatinib and nilotinib, but it is a common side effect of dasatinib, occurring in 14% to 30% of patients.[7,8] It is more common in patients:[7]

- On higher dosages of dasatinib
- With a history of heart disease, hypertension, rash, autoimmune disease and high cholesterol levels

This side effect may occur anywhere from 5 weeks to 1 year after the start of therapy.[7] Patients taking dasatinib must be monitored for the early signs of fluid retention, such as:[7,8]

- Dry cough
- Shortness of breath
- Tight chest

Early intervention is critical; refer any patient with symptoms of fluid retention to a doctor for immediate care.[8] Advise patients to weigh themselves regularly and report any weight gain ≥5 lbs (2.27 kg).[14] Central fluid retention in or around the lungs, stomach, central body tissues, heart, lungs, or brain – often associated with rapid weight gain – is potentially life-threatening.[8-10]

References

1. Imatinib product monograph. Novartis Pharmaceuticals Canada Inc., December 31, 2008.
2. Dasatinib product monograph. Bristol-Myers Squibb. January 20, 2009.
3. Nilotinib product monograph. Novartis Pharmaceuticals Canada Inc., September 5, 2008.
4. Krause DS, Va Etten RA. Tyrosine kinases as targets for cancer therapy. New Engl J Med 2005;353:172-187.
5. Fausel C. Targeted chronic myeloid leukemia therapy: seeking a cure. J Managed Care Pharm 2007;13(Suppl A):S8-12.
6. McFarland KL, Wetzstein GA. Chronic myeloid leukemia therapy: focus on second-generation tyrosine kinase inhibitors. Cancer Control 2009;16:132-140.
7. NCCN Clinical Practice Guidelines in Oncology. Chronic Myelogenous Leukemia. V2, 2009. Accessed online at: www.nccn.org/index.asp
8. Quintás-Cardama A, Cortés JE, Kantarjian H. Practical management of toxicities with tyrosine kinase inhibitors in chronic myeloid leukemia. Clin Lymphoma Myeloma 2008;8(suppl3):S82-S88.
9. Etienne G, Cony-Makhoul P, Mahon F-X. Imatinib mesylate and gray hair. N Engl J Med 2002;347:446.
10. Cortes J, O'Brien S, Quintas A, Giles F, et al. Erythropoietin is effective in improving the anemia indiced by imatinib mesylate therapy in patients with chronic myeloid leukemia in chronic phase. Cancer 2004;100:2396-2402.
11. Richardson G, Dobish R. Chemotherapy-induced diarrhea. J Oncol Pharm Pract 2007; 13:181-198.
12. Regroupement des pharmaciens en oncologie. General information for patients. Protocol: Erlotinib. Conseil de lutte contre le cancer. APES. GEOQ. September 2005.
13. Saltz LB. Understanding and managing chemotherapy-induced diarrhea. Supportive Oncology 2003;1:35-46.
14. Khoury HJ, Guilhot F, Hughes TP, Kim DW, et al. Dasatinib treatment for Philadelphia chromosome-positive leukemias. Cancer 2009;115:1381-94.
15. Guilhot F. Indications for imatinib mesylate therapy and clinical management. The Oncologist. 2004;9:271-281.
16. Deininger MWN, O'Brien SG, Ford JM, Druker BJ. Practical management of patients with chronic myeloid leukemia receiving imatinib. J Clin Oncol. 2003;21:1637-1647.
17. Peréz-Soler R, Delord JP, Halper A, Kelly K, et al. HER1/EGFR inhibitor-associated rash: future directions for management and investigation outcomes from the HER1/EGFR inhibitor rash management forum. The Oncologist. 2005;10:345-356.
18. Lynch TJ, Kim ED, Eaby B, Garey J, et al. Epidermal growth factor receptor inhibitor-associated cutaneous toxicities: an evolving paradigm in clinical management. The Oncologist 2007;12:610-621.
19. Segaert S, Custem EV. Clinical signs, pathophysiology, and management of skin toxicity during therapy with epidermal growth factor inhibitors. Annals of Oncology 2005;16:1425-1433.
20. The Abramson Cancer Center of the University of Pennsylvania. Imatinib. OncoLink. 2009. Accessed at: www.oncolink.org.

Overview of c-Kit inhibitors

This chapter contains information on the prevention and management of common side effects of multi-targeted kinase inhibitors (MKIs) that you are likely to encounter among cancer patients in your practice.

There are no evidence-based guidelines on how to manage MKI-induced side effects. The recommendations presented here are based on a review of expert opinion and best practices in oncology. For a complete description of all side effects of these agents, please consult the product monographs.[1,2]

c-Kit inhibitors

Imatinib (Gleevec®)
Sunitinib (Sutent®)

Two oral medications are available that inhibit the action of tyrosine kinases (TKs) on stem cell factor (c-Kit) receptors.[1,2] While these medications also target other TKs, this chapter focuses on inhibition of the c-Kit signaling pathway in the treatment of patients with gastrointestinal stromal tumours (GIST).[1,2] Nilotinib (see Bcr-Abl inhibitors) is currently under investigation for the treatment of GIST.

c-Kit in cancer

The c-Kit or KIT protein is a transmembrane cell receptor. Because it binds to stem cell factor, it is also called the stem cell factor receptor. When stem cell factor binds to c-Kit, it activates a cell-signaling cascade that induces:[3]

- Cell growth
- Cell differentiation
- Cell survival

c-Kit mutations are present in about 95% of GIST cells. These mutations enable the c-Kit receptor to activate independently and send growth signals into the cell without binding to stem cell factor.[3] Hence, GIST cells are able to grow, proliferate, and survive without stem cell factor regulation.[3]

A number of genetic mutations can alter the c-Kit receptor, activating the continuous transmission of growth signals within GIST cells. Some research suggests that the site of c-Kit mutation may have prognostic significance, and mutational analysis may provide clues to tumour aggressiveness and potential response to therapy.[3]

Drug administration

Imatinib

- Advise patients to take imatinib during a meal once or twice daily, as required, with a glass of water. Patients unable to swallow the tablets can drop them into a glass of water or apple juice, stir until they are disintegrated, and drink immediately. Leftover traces must be consumed.[1]

How to take imatinib

- Take imatinib with food to avoid nausea and vomiting.[4]
- Use caution when taking acetaminophen (e.g., Tylenol®) with imatinib, due to an increased risk of hepatotoxicity.[1]

Sunitinib

- This medication is taken once daily – with or without food. Sunitinib is administered on a 4-week on treatment, 2-week off treatment schedule.[2]

Patients should avoid grapefruit, grapefruit juice, star fruit, pomegranate juice, and Seville oranges, which may alter plasma levels, when taking either c-Kit inhibitor.[1,2]

If patients miss a dose of either medication, they should take it as soon as possible on the same day; however, if it is almost time to take their next dose, they should skip that dose and go back to their regular dosage schedule. They should not double doses on the next day.[1,2]

Mechanism of action

c-Kit inhibitors are small molecules that directly inhibit the activity of tyrosine kinases (TKs) on c-Kit receptors. They bind to receptor TKs to prevent ATP or other substances from interacting with these enzymes, shutting down cell-signal transmission.[1-3]

Imatinib

Imatinib inhibits the activity of TKs on c-Kit receptors. In GIST cells, it binds to the ATP site on c-Kit receptors to interrupt cell signaling. By blocking this site, imatinib prevents the TK from biochemically activating signaling proteins within the cell. Imatinib:[1,4]

- inhibits abnormal signaling
- inhibits cell proliferation
- induces cell death

Imatinib also inhibits the Bcr-Abl TK in chronic myeloid leukemia and TK receptors for platelet-derived growth factor (PDGF).[1]

Sunitinib

Sunitinib targets different signaling pathways to block the activity of a number of TKs that are implicated in tumour growth and spread. Like imatinib, in GIST, sunitinib targets the TK of c-Kit receptors. It also inhibits the TKs of VEGF, disrupting the growth of new blood vessels that feed tumours, and targets signaling pathways mediated by platelet-derived growth factor (PDGF), which may play a role in GIST.[2,3,5] Sunitinib also blocks the activity of FMS-like TK-3 (FLT3), colony stimulating factor receptor (SCF-1R), and neurotrophic factor receptor (RET).

By disrupting abnormal cell signaling, sunitinib inhibits the:[2,5]

- Growth and proliferation of GIST cells
- New blood-vessel growth in and near tumours
- Migration of cancer cells

Basic pharmacokinetics

Imatinib and sunitinib are metabolized primarily via the CYP3A4 pathway in the liver.[1,2] These medications interact with a host of CYP3A4 inducers, inhibitors, and substrates.[1,2] Imatinib also interacts with the CYP2D6 metabolic pathway.[1,2]

Sunitinib can prolong the QT interval and PR interval, and decrease heart rate. Patients who take drugs with dsyrhythmic potential or drugs that prolong the PR interval, including beta-blockers, calcium channel blockers, digitalis, or HIV protease inhibitors, must use caution when taking sunitinib.[2]

Prevention and management of common side effects

Most patients who are treated with c-Kit inhibitors have side effects.[1] Because they target different cell signaling pathways, the types and incidence of side effects vary for these medications. For example, fluid retention is a very common side effect of imatinib, while hand-foot skin reaction is very common in patients taking sunitinib.[1,2] The following table summarizes very common and common side effects of each medication.[1,2,7]

Skin or hair colour changes

Imatinib

- A small percentage of patients on imatinib may experience a repigmentation of grey hair.[8]

Sunitinib

- Skin or hair colour changes, particularly a yellowing or complete loss of color, can occur after the first week of sunitinib. Assure your patients that this side effect is reversible when therapy ends.[6]

Very common and common side effects of c-Kit inhibitors

Click on side effects highlighted in blue for more information and click on the arrow to return.

Imatinib

Very common

Cardiovascular disorders

- **Fluid retention**, e.g., swelling around eyes, weight gain

Gastrointestinal disorders

- Abdominal pain, **diarrhea**, indigestion, nausea, vomiting,

General disorders

- Bone, muscle, & joint pain
- Fatigue
- Headache
- Muscle cramps

Skin disorders

- **Rash**, **pruritis**

Common

Gastrointestinal disorders

- Abdominal swelling, constipation, gas, gastritis, heartburn, loss of appetite, mouth sores, taste disturbance, weight loss

General disorders

- Allergies, bleeding or bruising, chills, dizziness, hair loss, hot flushes, infections, insomnia, nose bleeds, night sweats, numbness, tingling, weakness

Eye disorders

- Blurred vision, conjunctivitis, dry eye, increased tears

Musculoskeletal disorders

- Joint swelling, muscle tension

Skin disorders

- Loss of skin sensitivity, sun sensitivity

Sunitinib

Very common

Blood disorders

- Low white blood cell and platelet counts

Cardiovascular disorders

- **Hypertension**

Gastrointestinal disorders

- Constipation, **diarrhea**, loss of appetite, mouth pain or irritation, nausea, **stomatitis**, taste disturbances, upset stomach, vomiting

General disorders

- Fatigue, headache

Skin disorders

- **Hand-foot skin reaction**, **rash**, hair colour change, skin discolouration

Common

Bleeding disorders

- Nose bleed

Cardiovascular disorders

- Swelling

Gastrointestinal disorders

- Abdominal pain

General disorders

- Dizziness, weakness

Infection

Skin disorders

- Dry skin

Refer for medical attention: imatinib

Tell patients with these common symptoms to consult their doctor:[1]

- Localised edema (swelling or pain in one part of the body)
- Low blood cell count (weakness; spontaneous bleeding or bruising; frequent infection with sore throat, chills, sore mouth or mouth ulcers)
- Peripheral edema (rapid weight gain, facial swelling or other signs of fluid retention)

Tell patients with these uncommon symptoms to see their doctor immediately: [1]

- Acute respiratory failure or pulmonary fibrosis (difficult or painful breathing, cough)
- Cellulitis (acute skin swelling)
- Cerebral edema, increased cranial pressure, stroke (severe headache, weakness or paralysis, seizures, difficulty speaking)
- Difficulty hearing
- Eye disorders (sudden change in eyesight or visual impairment)
- Gastrointestinal disorders (stomach pain, nausea, tarry dark stools or bloody urine)
- Heart disorders (crushing chest pain or irregular heartbeat)
- Hematologic disorders (bruising)
- Lightheadedness, dizziness or fainting
- Liver disorders (yellowing skin or eyes, light-coloured urine, loss of appetite, nausea)
- Potassium imbalance (muscle weakness, muscle spasms, abnormal heart rhythm)
- Raynaud's syndrome (cold or numb fingers or toes)
- Urinary tract infection (low urine output, thirstiness)

Tell patients with these rare side effects to seek emergency care:1

- Avascular necrosis or hip osteonecrosis (painful hips, difficulty walking)
- Inflammatory bowel disease (nausea, diarrhea, vomiting, abdominal pain, fever)
- Low red blood cells (pale skin, fatigue, breathlessness, dark urine)
- Serious skin disorders (severe rash, blistering or peeling skin, raised red or purple skin patches, itchy burning rash)

Refer for medical attention: sunitinib

Tell patients with any of the following constellations (groupings) of symptoms to see their doctor immediately:[2]

- Bleeding problems (blood in urine or stool; nose bleeds) and infection
- Blood clots (severe pain, swelling, or redness in legs or severe chest pain with shortness of breath)
- Heart problems (shortness of breath, fatigue, swollen feet and ankles)
- Low thyroid function (fatigue, constipation, dry skin, weight gain)
- Low white blood cell count (Infection, fever, bleeding)
- Myopathy or rhabdomyolysis (muscle aches or weakness, dark urine)
- Pancreatitis (abdominal pain, fever, nausea, vomiting)

When to stop sunitinib

Tell patients with rapid, pounding, or irregular heartbeat, dizziness, fainting, or seizures to stop taking sunitinib and seek emergency care.[2]

Hand-foot skin reaction (HFSR)

About 14% of patients taking sunitinib for GIST develop hand-foot skin reaction (HFSR), also known as hand-foot syndrome and palmar-plantar erythrodysesthesia.[2]

Prevention

During the first 2–4 weeks of therapy, prevention of traumatic activity and rest are crucial.[9] Urge your patients to:[9,10]

- Have a manicure or pedicure to remove thickened skin or calluses; follow with moisturizing cream
- Use a moisturizing cream
- Wear loose-fitting, soft shoes or slippers, foam absorbing soles, gel inserts to cushion pressure points, cotton socks
- Cushion callused areas with soft or padded shoes
- Reduce exposure of hands and feet to hot water (showers, dishwashing, etc.)
- Avoid excessive friction to hands or feet when performing tasks
- Avoid vigorous exercise or activities that place undue stress on the hands and feet
- Wear thick cotton gloves or socks to protect hands and feet and keep them dry
- Report any signs or symptoms of HFSR immediately to ensure early-stage treatment

Management

OTC therapy

Grade 1 (Mild; Discomfort, no disruption of activities)[9]

Advise patients to add the following:[9-11]

- Avoid hot water; cool water or cold compresses may ease symptoms
- Diligently apply moisturizers to keep palms and soles soft and pliable to prevent cracks or breaks in skin integrity
  - Use moisturizing creams twice daily
  - Use aloe vera lotion
  - Use 20% to 40% urea cream or 6% salicylic acid on callused areas
- Soak feet in magnesium sulfate (Epsom salts) to soften calluses and reduce pain on pressure
- Use low to moderate dose pain killers

Advise patients to consult their doctor about reducing their dosage of MKI, if symptoms of HFSR worsen after being treated for 2 weeks[9]

Prescribed therapy

Grade 2 (Moderate; Disrupts daily activity)[7]

Add the following:[9]

- Topical corticosteroid (e.g., clobetasol 0.05% ointment)
- 2% lidocaine topical ointment
- Oral NSAIDS, codeine, pregabalin, for pain
- Dose modification is required
- If symptoms worsen after 2 weeks, treatment interruption may be required

Grade 3 (Severe)[9]

- Treat as Grade 2
- Further dose modification is required
- If symptoms worsen after 2 weeks, treatment interruption may be required

For thick, tender sores after acute rash with/without blisters resolves:[9]

- 40% urea cream
- Tazarotene 0.1% cream
- Fluorouracil 5% cream

Key facts: HFSR

HFSR has a serious impact on the physical, psychological, and social well-being of patients who receive sunitinib.[9-13] **The look and onset of this reaction is different than capecitabine-induced HFSR**. The typical pattern of localized sensitive lesions with skin thickening, surrounded by redness, differs from classic HFSR, in which symmetrical changes in skin sensation, redness and swelling occurs.[8] Treatment may require dosage adjustment or the interruption of life-prolonging therapy in cancer patients.[9,10]

Most cases of HFSR are mild to moderate, but about 5% to 6% of patients develop a severe reaction that impairs daily-living activities.[9,10,12,13] These patients may experience extreme tenderness of the hands and feet – enough to affect hand or foot function and disrupt their quality of life.[13]

HFSR usually occurs within the first 2 to 4 weeks of therapy.[9] Tender, scaly sores – with or without blistering – appear on the palms and soles. The edges of thickened skin patches on fingertips, toes, and other pressure or flexure points, such as elbows or knuckles, may be surrounded by a swollen, reddish halo.[9,11,13] The hands or feet may tingle or feel sensitive to touch or heat.[11]

After several weeks, thickened, callus-like skin develops over the sores. These areas are usually painful and impair range of motion, function, and weight bearing.[9]

There are no evidence-based guidelines for the management of c-kit-related HFSR. Experts recommend prevention, early detection, and immediate treatment as crucial steps in the management of HSFR to prevent the withdrawal of life-prolonging c-kit therapy.[10] The management of moderate to severe HFSR requires dose modification and a temporary interruption of c-kit therapy until symptoms resolve. The patient's doctor may then reintroduce the c-kit inhibitor at a low dose and slowly escalate the dose to achieve therapeutic benefits without triggering a recurrence of HSFR.[10]

Skin products in use for HFSR

- Cetaphil® skin cleansers
- Aveno® shower gel
- Udderly Smooth®, Gold Bond®, Aveeno® lotions
- Norwegian Formula moisturizer and foot cream (Neutrogena®)
- Bag Balm®
- Eucerin® cream and Dry Skin Therapy
- Aquaphor® Healing Ointment
- Kerasal®
- Sunblock

Fluid retention

Fluid retention (edema) affects up to 81% of patients taking imatinib for GIST.[1]

Prevention

Advise your patients to:[9]

- Limit salt intake

For swollen eyelids or swelling around eyes:[9]

- Elevate head during sleep

Management

OTC therapy

Mild peripheral fluid retention

- For swelling around eyes, use skin-tightening agents, e.g., topical Preparation H® containing phenylephrine or lanolin (avoid eye contact)[9]

Prescribed therapy

Mild peripheral fluid retention

- Topical eye ointments with phenylephrine 0.25%[9,12]
- Topical corticosteroid (e.g., hydrocortisone 1%)[9,12]

Moderate fluid retention

- Low-dose loop diuretic, e.g., furosemide with calcium and magnesium supplements[9]
- Close electrolyte monitoring[9]

Key facts: Fluid retention

Peripheral fluid retention (edema) is usually superficial and mild to moderate in nature. Its occurrence is dose-related. The most frequent form of fluid retention is swollen eyelids or swelling around the eyes (periorbital or periocular edema), which is more pronounced in the morning and often associated with swelling of ankles, feet and lower legs.[14-16] This side effect may also occur among patients taking sunitinib.[11] It does not usually require treatment.[11]

Peripheral fluid retention tends to improve over time.[14] It occurs more frequently in:[16]

- Women
- Adults over 65 years of age
- Patients with a history of heart or kidney problems

Early intervention is critical; refer any patient with symptoms of fluid retention to a doctor for care.[14] Advise patients to weigh themselves regularly and report any weight gain ≥5 lbs (2.27 kg).[11] Generalized fluid retention in or around the lungs, stomach, central body tissues, heart, lungs, or brain – often associated with rapid weight gain – is potentially life-threatening.[14-16]

Hypertension

Hypertension develops in about 14% of patients with GIST who are treated with sunitinib.[2]

Monitoring	Encourage patients to: • Monitor their blood pressure (BP) weekly for the first 6 weeks of treatment then on a regular basis[17] • Keep a diary of blood-pressure readings[5]	
Management	Advise patients with uncontrolled hypertension to see their doctor immediately for treatment.[2,17]	**Prescribed therapy** • Most hypertension can be managed with standard antihypertensive therapy, taking into account possible drug interactions.[2,5,17] • Discontinuation of therapy for severe or persistent hypertension despite treatment[2]

Key facts: Hypertension

Like other anti-angiogenic agents that inhibit VEGF, sunitinib may cause a significant and sustained increase in blood pressure (BP).[19] Patients who receive this medication should be monitored for the onset or worsening of hypertension.[2]

Hypertension may develop in the first few weeks of therapy or slowly over time. Patients with sunitinib-induced hypertension may develop proteinuria and should be screened for this side effect.[5,18]

Hypertension is usually mild to moderate and manageable with standard antihypertensive therapy. About 4% of patients with GIST develop moderately severe or severe hypertension.[13] Lifestyle modification is recommended for all patients with hypertension.[5,17,18]

Rash

Rash is a common side effect of imatinib and sunitinib.[1,2] It occurs in about 45% of patients with GIST on imatinib and in about 15% of those on sunitinib.[1,2,6]

Prevention

A proactive approach is critical in managing rash. When patients begin therapy, advise them to:[19-21]

- Cleanse with mild soaps or cleaners or bath or shower oils to avoid skin dryness.
- Moisturize twice a day with a colloidal oatmeal lotion, such as Aveeno® lotion, or with thick, emollient-based creams, such as Neutrogena® Norwegian Formula hand cream, or Vaseline Intensive Care® Advanced Healing Lotion.
- Use only fragrance- , alcohol-, and dye-free lotions and cosmetics.
- Use a dermatologist-approved cover-up, such as Dermablend® or Cover FX®, to conceal the rash.
- Remove make-up with a gentle, skin-friendly cleanser, e.g., Neutrogena®, Dove®
- Use a broad-spectrum sunscreen (SPF 15 or greater) that contains zinc oxide or titanium dioxide.

Management

OTC therapy

Mild to moderate rash[14-16]

- Antihistamine (diphenhydramine)
- Topical steroid (hydrocortisone 0.5%)
- Coal tar preparations

Prescribed therapy

Moderate to severe rash[6,15]

- Topical corticosteroid (e.g., hydrocortisone 2.5%)
- Oral corticosteroids, such as prednisone 1 mg/kg daily with or without topical triamcinolone acetonide 0.1% ointment[14]
- Topical clindamycin[6]
- Temporary interruption of imatinib therapy until resolution of rash with a rechallenge at low dose[14-16]

Key facts: Rash

Among imatinib-treated patients, rash is more likely to occur in women and patients on higher doses.[15] In the most common type of imatinib-induced rash, skin spots and bumps appear on the forearms, trunk, and, sometimes, the face. They are often itchy, and may become infected and crusty, if scratched. This generalized rash is usually mild and, in most cases, self-limited – it has a natural lifespan.[15]

When to stop imatinib

Tell any patient who develops a severe, blistering rash or red welts with purple areas to stop imatinib and seek immediate care.[1,22]

Rash may occur after 3 to 4 weeks of sunitinib.[16] This rash is similar to EGFR-induced rashes – albeit less frequent and milder – with spots and bumps on the upper chest, back or face that may or may not contain sterile fluid.[6] Generalized skin rashes are usually mild to moderate, tend to decrease over time, and rarely require dose reduction.[6,17]

There are no evidence-based guidelines for the treatment of c-Kit inhibitor-induced rash. Early recognition of symptoms and a prompt start of symptomatic therapy are the mainstays of treatment. Mild to moderate symptoms are managed while the patient remains on therapy. If necessary, patients on imatinib may stop therapy until a severe rash resolves. Refer any patient who develops a severe rash to a doctor for evaluation and treatment.[6,15]

Pruritis

Pruritis (itchiness) is a common side effect of imatinib.[1]

Prevention

To prevent dry skin, a common cause of itchiness, advise your patients to:[5]

- Use mild soaps that contain no deodorants or fragrance, such as Dove® or Neutrogena®
- Frequently apply lotions or bland emollients, such as Eucerin® cream, Neutrogena® Norwegian Formula Hand Cream, or Vaseline Intensive Care® Advanced Healing Lotion
- Choose "anti-itch" products
- Use liquid shower gels instead of soap

Management

Mild to moderate pruritis
Advise patients to:[5]

- Apply more lotion than usual to help reduce or eliminate itchiness on the trunk or extremities
- Use lotions with aloe vera or dimethicone Moisturel®
- Use anti-dandruff shampoos and conditioners
- Use hair products that contain tea tree oil, which contain extra moisturizers and may relieve symptoms

Refer to doctor for intense, widespread itching

Antihistamines may provide some relief[14-16]

Key facts: Pruritis

Pruritis or itchiness is the consequence of loss of skin moisture.[23] In patients treated with imatinib, it is usually associated with rash or xerosis.[1] It may be disruptive during sleep or waking hours.[5]

Stomatitis

Stomatitis (mouth inflammation) is a symptom of mucositis, a common side effect of sunitinib, occurring in about 16% of patients with GIST.[2] This side effect is uncommon in patients taking imatinib for GIST.[1] In patients on sunitinib, this side effect may lead to dosage reductions that limit therapeutic benefit.[5]

Prevention

Advise patients to:[24,25]

- Avoid cheek or lip biting
- Avoid mouth breathing
- Maintain good oral hygiene
- Maintain dentures by brushing daily and soaking in antimicrobial solution for at least 30 minutes/day and rinse thoroughly
- Avoid spicy and highly textured foods
- Avoid highly flavoured and alcohol-containing mouthwashes

Management		
	OTC therapy For mild cases of mouth sores, pain, or redness on the inner cheeks, tongue, or lips Meticulous oral hygiene:[24,25] • Toothbrushing, 3-4 times daily with soft-bristle toothbrush. Soak toothbrush in warm water to soften bristles • If brushing is painful, Toothettes (sponge-tipped stick with toothpaste), sponges, or gentle use of Waterpik® • Biotene toothpaste is non-irritating and contains natural salivary enzymes to control bacteria • Floss gently once daily to avoid gum injury • Salt and baking-soda rinses (1/2 teaspoon of each ingredient in 1 cup of warm water at least 4 times daily, especially after meals) • Bland rinses, antimicrobial mouthwash • OTC analgesics, such as ibuprofen (e.g., Advil®, Motrin®) and acetaminophen (e.g., Tylenol®) **Refer to doctor if patient has difficulty eating or drinking sufficient fluids or if redness is associated with lesions on the inner cheeks, tongue or lips**[26]	**Prescribed therapy** (moderate to severe cases): • Topical fluoride (dentist)[24] • Topical anesthetics[24] • Corticosteroid solution[25] • Topical or systemic analgesics[24] • Topical or systemic antifungals[25] • Palliative mixtures of various agents[24]

Key facts: Stomatitis

In patients treated with sunitinib, the integrity of mucous membranes may be compromised, leading to the swelling and reddening of membranes lining the mouth. Mouth sores or cankers may develop. Patients may complain of changes on the inner cheeks or mouth surfaces, even when mouth sores are not present or only a mild redness is evident. Patients may experience:[5]

- Difficulty chewing
- Mouth pain
- Painful swallowing (dysphagia)

Maintaining mucosal health, integrity, and function is crucial in patients with stomatitis. Aggressive intervention can make a significant impact on this side effect.[5] Treatment aims to relieve symptoms until the mucous membranes can rejuvenate, usually within 7 to 14 days. Smokers have a greater risk of stomatitis.[24]

There are no evidence-based guidelines for the prevention or treatment of c-Kit inhibitor-induced stomatitis, and experts tend to follow the clinical practice guidelines for chemotherapy- or EGFR-induced oral mucositis.[24-26]

Clinical practice guidelines stress the importance of oral hygiene in cancer patients, but due to a lack of supportive evidence, methods are usually based on personal preference and anecdotal experience.[24]

Good oral hygiene:[24,25]

- Reduces the severity of stomatitis
- Reduces mouth pain
- Reduces oral bleeding
- Reduces the risk of dental complications
- Minimizes the risk of soft tissue infections
- Enables patients to maintain a nutritious diet

The use of chlorhexidine mouth rinses is not recommended.
They contain alcohol and may sting. Dilution defeats their antibacterial benefits.[25]
Hydrogen peroxide rinses may worsen mouth ulcers.[25]

Topical preparations in widespread use for chemotherapy-induced stomatitis contain ingredients such as lidocaine, benzocaine, milk of magnesia, kaolin, pectin, and diphenhydramine. There is no significant evidence of the effectiveness or tolerability of these concoctions, and some may be only minimally better than saline rinses. Clinical trials in chemotherapy patients with stomatitis have shown no difference in the effectiveness of chlorhexidine mouthwash, "magic" mouthwashes that contain lidocaine, and salt-and-baking soda rinses.[24]

Diarrhea

Diarrhea is very common in imatinib-treated patients and common in sunitinib-treated patients with GIST.[1,2] Up to 65% of patients on imatinib and 41% of patients on sunitinib for GIST have diarrhea.[1,2] Dietary modifications are not recommended in anticipation of diarrhea.[27]

Prevention	No prevention measures are recommended.
Management OCT therapy **Refer to doctor if moderate diarrhea does not improve after 24 hours of treatment**	Aggressive use of loperamide (e.g., Imodium®) for early-onset diarrhea **Mild to moderate (less than 4 loose stools per day)** • Follow instructions on package insert: 2 tablets immediately, then 1 tablet after each liquid bowel movement (maximum: 8 tablets/24 hours) **Moderate (more than 4 to 6 loose stools per day or night-time diarrhea)** • 2 tablets immediately, then 1 tablet every 2 hours during the day and 2 tablets every 4 hours during the night until bowel movements are normal for at least 12 hours • **This dosage is higher than packaging recommendations. Advise your patients that it is important to take the medication at higher doses to stop diarrhea**
Replace lost fluids[22,27]	• Fluid intake is more critical than food intake in patients with diarrhea. To replace lost fluid, advise patients with no contraindication to increase intake by up to 3 to 4 litres per day. • Drink several types of fluid, including plain water and electrolyte-containing drinks, such as clear broth, gelatin desserts, sports drinks, flat soft drinks, or decaffeinated tea
Anal care[22]	Advise patients to: • Clean the anal area with mild soap and warm water after each bowel movement to prevent irritation • Apply a barrier cream or ointment, such as petroleum jelly or Isle's paste • Soak in a warm bathtub or sitz bath to relieve discomfort • Examine the anal area for red, scaly or broken skin
Diet[5,28]	Advise patients to: • Advise patients to eat and drink small quantities of food often • Avoid spicy, greasy, or fried foods • Follow the BRAT (banana, rice, applesauce, toast) diet, along with clear liquids, until diarrhea begins to resolve • Avoid cabbage, Brussels spouts, and broccoli, which may produce stomach gas, bloating and cramps

Key facts: Diarrhea

There are no evidence-based guidelines for the prevention or treatment of diarrhea in patients taking c-Kit inhibitors. Antidiarrheal medications are usually able to control this dose-related side effect.[14]

- Loperamide is standard in mild to moderate cases at dosage intervals and levels recommended for uncomplicated EGFR- and chemotherapy-induced diarrhea.

When patients seek OTC treatment for diarrhea, it is important to ask them about:[27-29]

- Number of stools per day and stool composition, e.g., watery, presence of blood, nocturnal
- Presence of diarrhea before their last treatment
- Medication profile to identify other agents that may contribute to diarrhea
- Dietary profile
- Signs and symptoms of complicated diarrhea, including:
  - Blood in stool
  - Dehydration, e.g., oral dryness, low urine production or dark yellow urine, weight loss, dry eyes or mouth, sunken eyes, low pulse, dizziness or feeling faint when getting up
  - Fever
  - Lethargy or altered mental state
  - Nausea and vomiting
  - Signs of infection
  - Stomach cramps

References

1. Imatinib product monograph. Novartis Pharmaceuticals Canada Inc., December 31, 2008.
2. Sunitinib product monograph. Pfizer Canada. August 13, 2008.
3. Din OS, Woll PJ. Treatment of gastrointestinal stromal tumours: focus on imatinib mesylate. Therapeut Clin Risk Management 2008;4:149-162.
4. Krause DS, Va Etten RA. Tyrosine kinases as targets for cancer therapy. New Engl J Med 2005;353:172-187.
5. Wood LS. Managing the side effects of sorafenib and sunitinib. Comm Oncol 2006;3:558-562.
6. Rosenbaum SE, Wu S, Newman MA, West DP, et al. Dermatologic reactions to the multitargeted tyrosine kinase inhibitor sunitinib. Support Care Cancer 2008;16:557-566.
7. McFarland KL, Wetzstein GA. Chronic myeloid leukemia therapy: focus on second-generation tyrsone kinase inhibitors. Cancer Control 2009;16:132-140.
8. Etienne G, Cony-Makhoul P, Mahon F-X. Imatinib mesylate and gray hair. N Engl J Med 2002;347:446.
9. Lacouture ME, Wu S, Robert C, Atkins MB, et al. Evolving strategies for the management of hand-foot skin reaction associated with the multitargeted kinase inhibitors sorafenib and sunitinib. The Oncologist 2008;13:1001-1011.
10. Anderson R, Jatoi A, Robert C, Wood LS, et al. Search for evidence-based approaches for the prevention and palliation of hand-foot skin reaction (HFSR) caused by the multikinase inhibitors. The Oncologist 2009;14. Published online March 22, 2009.
11. Managing side effects of kit inhibitors. Caring for Oncology Patients: Tips and Tools for managing targeted therapy. Little Falls, NJ; Projects in Knowledge Inc., 2009.
12. Rosenbaum SE, Wu S, Newman MA, West DP, et al. Dermatological reactions to the multitargeted tyrosine kinase inhibitor sunitinib. Support Cancer Care 2008;16:557-566.
13. Lacouture ME, Reilly LM, Gerami P, Guitart J. Hand foot skin reaction in cancer patients treated with the multikinase inhibitors sorafenib and sunitinib. Ann Oncol 2008;19:1955-1961.
14. Quintás-Cardema A, Cortés JE, Kantarjian H. Practical management of toxicities with tyrosine kinase inhibitors in chronic myeloid leukemia. Clin Lymphoma Myeloma 2008;8(suppl3):S82-S88.
15. Guilhot F. Indications for imatinib mesylate therapy and clinical management. The Oncologist. 2004;9:271-281.
16. Deininger MWN, O'Brien SG, Ford JM, Druker BJ. Practical management of patients with chronic myeloid leukemia receiving imatinib. J Clin Oncol. 2003;21:1637-1647.
17. Hutson TE, Figlin RA, Kuhn JG, Motzer RJ. Targeted therapies for metastatic renal cell carcinoma: an overview of toxicity and dosing strategies. The Oncologist 2008;13:1084-1096.
18. Managing side effects of multi-kinase inhibitors. Caring for Oncology Patients: Tips and Tools for managing targeted therapy. Little Falls, NJ; Projects in Knowledge Inc., 2009.
19. Peréz-Soler R, Delord JP, Halper A, Kelly K, et al. HER1/EGFR inhibitor-associated rash: future directions for management and investigation outcomes from the HER1/EGFR inhibitor rash management forum. The Oncologist. 2005;10:345-356.

20. Lynch TJ, Kim ED, Eaby B, Garey J, et al. Epidermal growth factor receptor inhibitor-associated cutaneous toxicities: an evolving paradigm in clinical management. The Oncologist 2007;12:610-621.
21. Segaert S, Custem EV. Clinical signs, pathophysiology, and management of skin toxicity during therapy with epidermal growth factor inhibitors. Annals of Oncology 2005;16:1425-1433.
22. Regroupement des pharmaciens en oncologie. General information for patients. Protocol: Erlotinib. Conseil de lutte contre le cancer. APES. GEOQ. September 2005.
23. Lacouture ME, Boerner SA, LoRusso PM. Non-rash skin toxicities associated with novel targeted therapies. Clinical Lung Cancer 2006;8(1):S36-S42.
24. Rubenstein EB, Peterson DE, Schubert M, Keefe D, et al. Clinical practice guidelines for the prevention and treatment of cancer therapy-induced oral and gastrointestinal mucositis. Cancer. 2004;100(9) suppl:2026-2046.
25. Rosenbaum EH, Silverman S, Festa B, Rosenbaum I, et al. Mucositis: chemotherapy problems and solutions. Cancer Supportive Care Programs. October 2007. Accessed online at: www.cancersupportivecare.com/drug.php.
26. Morse L, Calarese P. EGFR-targeted therapy and related skin toxicity. Seminars in Oncology Nursing 2006;22(3):152-162.
27. Richardson G, Dobish R. Chemotherapy-induced diarrhea. J Oncol Pharm Pract 2007;13:181-198.
28. Saltz LB. Understanding and managing chemotherapy-induced diarrhea. Supportive Oncology 2003;1:35-46.
29. Wadler S. Diagnosis and management of cancer-treatment-induced diarrhea. Clin Colorectal Cancer 2005;4:382-383.

Overview of Epidermal growth factor receptor inhibitors

This chapter contains information on the prevention and management of common side effects of epidermal growth factor receptor (EGFR) inhibitors that you are likely to encounter among cancer patients in your practice.

EGFR inhibitors

Erlotinib (Tarceva®)
Gefitinib (Iressa®)
Cetuximab (Erbitux®)
Panitumumab (Vectibix®)

There are no evidence-based guidelines on how to manage EGFR inhibitor-induced side effects. The recommendations presented here are based on a review of expert opinion and best practices in oncology. For a complete description of all side effects of these agents, please consult the product monographs.[1-4] Infusion reactions, which occur with intravenous (IV) agents, are usually encountered in the clinic or hospital setting and will not be described here.

Four medications are available that inhibit the action of EGFR.

- Erlotinib and gefitinib are oral medications with similar mechanisms of action and side-effect profiles.[1,2]
- Cetuximab and panitumumab are monoclonal antibodies that are administered by intravenous infusion in the hospital or clinic setting.[3,4]

EGFR in cancer

EGFR is a protein that crosses the cell membrane. This receptor is a member of the human epidermal growth factor receptor (HER) family. It is also referred to as HER1 and EGFR/HER1.[5,6]

EGFR and its ligands play a key role in the signal transduction pathways that regulate:[7]

- cell proliferation
- survival
- differentiation

In cancer cells, the overexpression of EGFR, overproduction of EGFR ligands, or presence of EGFR mutation triggers continuous EGFR signaling. The dysregulation of EGFR signal transduction pathways:[5,7]

- stimulates cancer cell proliferation
- prolongs cancer cell survival by blocking apoptosis (cell death)
- enhances cell mobility to promote cancer invasion and metastasis
- stimulates tumour-induced angiogenesis

Drug administration

Erlotinib

- Erlotinib is an oral medication, taken once daily.[1]

Gefitinib

- Gefitinib is an oral medication, taken once daily.[2]
- As of December 12, 2008, no new patients have been prescribed gefitinib. Health Canada stipulates that this indication is restricted to patients with EGFR-positive tumours who are currently benefiting from gefitinib.[2]

Cetuximab

- Cetuximab (once weekly) is administered as intravenous infusions in the hospital or clinic setting.[3]

Panitumumab

- Panitumumab (once every 2 weeks) is administered as intravenous infusions in the hospital or clinic setting.[4]

How to take EGFR inhibitors

- Take erlotinib (TARCEVA®) with a glass of water at least one hour before or two hours after a meal at the same time every day. Do not crush, cut, or chew the tablets. If you cannot swallow the tablet whole, dissolve it in 50 ml of water. Leftover traces must be consumed.[1]
- Gefitinib can be taken orally with or without food.[2]
- Patients can take a missed dose of gefitinib as long as they remember at least 12 hours before their next dose is due. If it is less than 12 hours until their next dose, they should skip that dose and resume their normal regimen on the next day. Patients who miss one or more doses of erlotinib should contact their doctor or pharmacist. Patients on either medication should never take a double dose on the day after missing a dose.[1,2]

Mechanism of action

Erlotinib, gefitinib

Erlotinib and gefitinib are small-molecule, tyrosine kinase (TK) inhibitors. They interrupt the continuous EGFR signaling in cancer cells by binding to the intracellular portion of EGFR to disrupt downstream signal transmission.[5,7] The inactivation of EGFR signaling pathways by erlotinib and gefitinib inhibits:[5]

- Cancer-cell proliferation
- Angiogenic growth factor production
- Tumour-induced angiogenesis
- Cancer-cell invasion

Cetuximab, panitumumab

Cetuximab and panitumumab are monoclonal antibodies that bind to the extracellular portion of EGFR to block other ligands from activating the EGFR signaling pathway. Blocking this pathway from outside the cell produces almost the same effects in cancer cells as small-molecule TK inhibitors that work inside the cell, inhibiting:[5]

- Cancer cell proliferation
- Angiogenic growth factor production
- Cancer cell invasion and metastasis

Lifestyle & medication
Cigarette smoking can reduce erlotinib exposure (area under the curve [AUC]) by 50% to 60%.[1]

Drug interactions
The solubility of erlotinib is pH-dependent. Drugs that alter the pH of the upper GI tract, such as omeprazole, reduce erlotinib exposure by 46%.[1]

Basic pharmacokinetics

Both oral drugs are primarily metabolized in the liver via the CYP3A4 pathway. They may interact with other inducers or inhibitors of this pathway, resulting in the alteration in plasma drug concentrations within the body.[1,2]

Erlotinib is metabolized, to a lesser extent via the CYP1A2 and CYP1A1 pathways. Smoking may induce metabolism via these pathways, thereby increasing the clearance of erlotinib.[1]

Prevention and management of common side effects

EGFRs are found on normal epithelial tissue, such as the skin, hair follicles, and lining of the gastrointestinal (GI) tract – which may explain why skin disorders and GI disturbances are the most common side effects of EGFR inhibitors.[6,8,9] The following table summarizes the most common side effects of EGFR inhibitors.[1,2]

Common side effects of EGFR inhibitors

Click on side effects highlighted in blue for more information and click on the arrow to return.

Eye disorders

- Conjunctivitis (pink eye)
- Keratoconjunctivitis sicca (dry eye)

Gastrointestinal disorders

- Abdominal pain
- Abnormal liver function tests
- Bleeding from stomach or intestine
- Blood in urine
- **Diarrhea**
- Nausea
- **Stomatitis** (mouth problems)
- Vomiting
- **Xerostomia** (dry mouth)

General disorders

- Anorexia
- Dizziness
- Fatigue
- Headache
- Loss of appetite
- Metabolism and nutritional disorders
- Nosebleeds

Infection

Respiratory disorders

- Cough
- Dyspnea

Skin disorders

- **Paronychia** (nail problems)
- **Pruritis** (itchy, red skin)
- **Rash**
- **Xerosis** (dry skin)

Refer for medical attention

- Patients with a persistent cough or fever who have sudden difficulty breathing should see a doctor immediately, as these symptoms may signal interstitial lung disease, a rare but serious side effect.[1] It can happen as early as 5 days and as late as >9 months after starting therapy.[10]
- Patients with signs of liver failure or gastrointestinal hemorrhage (tarry dark stools, bloody urine, or who cough up blood) must contact their doctor immediately.[1]

Rash

Rash occurs in more than 50% and up to 100% of patients treated with EGFR inhibitors (EGFRI).[11-13] Some evidence suggests that the early introduction of preventive strategies, including the prescription of oral antibiotics, may reduce the severity of skin reactions.[14] Most patients experience a mild to moderate rash; severe rash is uncommon.[9,12] Rashes tend to be more common and severe among patients who receive IV agents.[12]

Prevention

A proactive approach is critical in managing EGFRI-induced rash.[11] When patients begin therapy, advise them to:[9-12]

- Cleanse with mild soaps or cleaners or bath or shower oils to avoid skin dryness.
- Moisturize twice a day with thick, emollient-based creams, such as Aveeno® lotion, Neutrogena® Norwegian Formula hand cream, or Vaseline Intensive Care® Advanced Healing Lotion.
- Use only fragrance- , alcohol-, and dye-free lotions and cosmetics.
- Use a dermatologist-approved cover-up, such as Dermablend® or Cover FX®, to conceal the rash.
- Remove make-up with a gentle, skin-friendly cleanser, e.g., Neutrogena®, Dove®
- Use a broad-spectrum sunscreen (SPF 15 or greater) that contains zinc oxide or titanium dioxide.

Management	**Mild**[11] • Localized • Few symptoms • No impact on daily activities • No sign of infection	No treatment or: • Topical hydrocortisone 0.5% cream[11] • Mild soap and cleansers[6] • Moisturizers twice daily[6] **Advise patient to monitor the rash for changes in severity.**[1-4] **Refer to doctor if rash persists or worsens in severity.**[11]	**Prescribed medications:** • Topical agents with anti-inflammatory properties, such as hydrocortisone 1% to 2.5% cream, metronidazole cream or clindamycin 1% gel.[11]
	Moderate[11] • Generalized • Mild symptoms (e.g., pruritis, tenderness) • Minimal impact on daily activities	**Refer to doctor as soon as possible**	**Prescribed medications:**[8,11] • Hydrocortisone 2 .5% cream, clindamycin 1% gel, or pimecrolimus 1% cream PLUS • doxycycline (100-mg BID) or minocycline (100-mg BID)
	Severe[11] • Generalized • Severe symptoms (e.g., pruritis, tenderness) • Significant impact on daily living • Potential for infection	**Refer to doctor as soon as possible**	EGFRI dose reduction is recommended. **Prescribed medications:**[11] • Hydrocortisone 2.5% cream, clindamycin 1% gel, or pimecrolimus 1% cream PLUS doxycycline (100-mg BID) or minocycline (100-mg BID) PLUS methylprednisolone • Analgesics for patients with painful rash[12]

Key facts: Rash

The onset of rash usually occurs from 1 to 3 weeks after therapy begins.[6,12] The rash may wax and wane throughout therapy or peak 2 to 3 weeks after therapy begins.[6,9,12] In most patients, it tends to improve gradually but spontaneous resolution may occur.[5,9,12] In patients taking IV EGFR inhibitors, the rash may flare after each infusion.[12] With the discontinuation of therapy, the rash usually disappears in a few weeks, sometimes with residual hyperpigmentation (skin-colour changes) and dry skin.[12]

Encourage patients who are treated with topical agents to continue their use up to 7 days beyond the abatement of rash or as long as directed by their doctor.[11]

Often described as acne-like or acneiform, the rash develops as inflammatory papules or pustules on the face, neck, and upper torso.[6,9,12] The limbs, scalp, and lower torso are less often involved.[6] Rash may be accompanied by dry skin, pruritis (itchiness), or erythema (redness).[9]

There is no association between the severity of rash and type of skin or history of acne. The EGFRI-induced rash has an inflammatory rather than infectious origin.[12] Unlike acne vulgaris, no true comedones are seen.[12] The rash may undergo several stages:[12,15]

- Swelling, redness, burning sensation
- Formation of small, solid, round papules of less than 5 mm in diameter may evolve into pustules containing inflammatory (as opposed to infectious) material and cellular debris
- Yellowish crusting of drying pustules

EGFRI-induced rash is not acne vulgaris

- Traditional acne medications, such as benzoyl peroxide, retinoids and alpha-hydroxyacids, are not effective and may worsen this rash.[9,12]

Dosage adjustment may limit the benefits of therapy

- Since dosage adjustment may limit the benefits of therapy, management of rash is an important therapeutic goal.[15]
- EGFRI-induced rash appears to be dose-dependent,9,12 and data from several clinical trials suggest a positive correlation between rash and patient response and/or survival.[9]

Pruritis

In patients treated with EGFR inhibitors, pruritis is usually associated with EGFR-induced rash or xerosis.[9,12,16]

Prevention	Advise patients to use: • Mild soaps, such as Dove® or Neutrogena®[6,12] • Bland emollients, such as Eucerin® cream, Neutrogena® Norwegian Formula Hand Cream, or Vaseline Intensive Care® Advanced Healing Lotion[6,12]	
Management	Moderate to severe pruritis	**Refer to doctor for intense, widespread itching**[6] Antihistamines may provide some relief[6,12,16]

Key facts: Pruritis

Pruritis or itchiness is the consequence of loss of skin moisture.[16] Pruritis may be mild or localized, widespread or intense, or worsen to the point where it interferes with daily activities.[12]

Xerosis

Xerosis (dry skin) occurs in up to 35% of patients treated with EGFR inhibitors and more often in patients on gefitinib therapy.[17]

Prevention

Advise patients to:[9-12,15]

- Cleanse with mild soaps or cleaners or bath or shower oils to avoid skin dryness.
- Moisturize twice a day with a colloidal oatmeal lotion, such as Aveeno® lotion, or thick, emollient-based creams, such as Neutrogena® Norwegian Formula hand cream, or Vaseline Intensive Care® Advanced Healing Lotion.
- Use only fragrance-, alcohol-, and dye-free lotions and cosmetics.
- Remove make-up with a gentle, skin-friendly cleanser, e.g., Neutrogena®, Dove®

Management

First signs of skin dryness Dry skin on face, back, chest	Advise patients to: • Discontinue the use of lotions or gels that contain alcohol at the first signs of dryness[12] • Switch to oil-in-water creams[12]
Moderate to severe xerosis Dry skin on limbs	Greasy, water-in-oil creams or ointments[12]
Eczema	Short-term use (1-2 weeks) of weak topical corticosteroid creams[12] **Refer to doctor if uncontrolled by OTC treatment**
Infection	Topical antibiotics[12] **Refer to a doctor if uncontrolled by OTC treatment**
Skin fissures	Treatment options[16] • 50% propylene glycol under a plastic bandage • Salicylic acid 10% ointment • Colloid dressing **Refer to doctor for treatment if not controlled by OTC treatment**

Key facts: Xerosis

Apart from general hydrating measures, choice of the right treatment is critical to alleviate skin dryness. The frequent application of emollients that contain ammonium lactate, e.g., Hydrolac or Lac-Hydrin, or 5% to 10% urea, e.g., Eucerin 5, or Uremol 10, may substantially improve xerosis.[18] Advise patients to avoid occlusive topical creams and lotions that can obstruct hair follicles, which may lead to infection.[12,18]

The dry, scaly, itchy skin, which resembles atopic eczema, usually begins between one week to 3 months after the start of therapy.[6,12] It is persistent and often lasts several months.[16]

Xerosis tends to worsen with:[12,16,17]

- Older age
- Prior history of atopic eczema
- Previous treatment with cytotoxic agents

The dry, scaly skin appears on the limbs, torso and areas of EGFRI-induced rash. Xerosis often affects the fingertips, heels, and toes. Painful fissures may develop in these areas, in nail folds and over finger joints in excessively dry skin – a condition that can make wearing shoes or performing tasks difficult for patients.[12,16-18]

Dry skin may become increasingly fragile and bruise easily. Xerosis may worsen, becoming chronically red and irritable. Secondary infection with ***S. aureus*** may occur.[12,17]

Paronychia

Paronychia is a painful inflammation that occurs around finger and toe nails in up to 19% of patients treated with EGFR inhibitors.[1-4] It typically appears within 4 to 8 weeks or up to 6 months after therapy begins.[17]

Prevention

Advise your patients to:

- Wear comfortable, loose-fitting shoes to avoid friction or pressure on nail folds[12,17]
- Avoid biting nails or cutting them too short[17]

Management

OTC treatment

- Topical antiseptics or antibiotics (soaks or creams) to prevent or treat mild infection[12]
- Epsom salts or Buro sol (aluminum acetate) soaks daily[6]
- Weekly application of topical silver nitrate to treat hamburger-like bumps[12]
- Foot cushioning products for extra comfort[12]

Refer to doctor for pain in nail bed, nail loss, signs of infection[6,12]

Prescription medication

- Topical antimicrobials, such as mupirocin and nystatin ointment[17]
- Topical corticosteroid, such as 1% triamcinolone ointment[17]
- Doxycycline, 6-week course of 100 mg twice daily[17]

Key facts: Paronychia

Although not infective in origin, EGFRI-induced paronychia makes nails more sensitive to infection.[12] Nails tend to grow slower, become brittle, and crack.[16]

Paronychia can be painful and mimic an ingrown nail.[12] It may interfere with simple manual work or prevent the patient from wearing any shoes but sandals.[16] It may take weeks to heal and may not resolve unless therapy stops for a short period or ends.[6,16] In severe cases, abscesses and small, red, oozing, and bleeding bumps that look like raw hamburger meat develop in nail folds.[16]

Refer to a dermatologist or family physician

A podiatrist cannot provide adequate foot care in this context.

Diarrhea

Diarrhea is a very common side effect of all EGFR inhibitors occurs in up to 54% of patients treated with EGFR inhibitors, especially the ones who take erlotinib.[1-4,19] Dietary modifications are not recommended in anticipation of diarrhea.[20]

Prevention	No prevention measures are recommended.
Management OCT therapy[19] **Refer to doctor if moderate diarrhea does not improve after 24 hours of treatment**	Aggressive use of loperamide (e.g., Imodium®) for early-onset diarrhea **Mild to moderate (less than 4 loose stools per day)** • Follow instructions on package insert: 2 tablets immediately, then 1 tablet after each liquid bowel movement (maximum: 8 tablets/24 hours) **Moderate (more than 4 to 6 loose stools per day or night-time diarrhea)** • 2 tablets immediately, then 1 tablet every 2 hours during the day and 2 tablets every 4 hours during the night until bowel movements are normal for at least 12 hours • **This dosage is higher than packaging recommendations. Advise your patients that it is important to take the medication at higher doses to stop diarrhea**
Replace lost fluids[19-21]	• Fluid intake is more critical than food intake in patients with diarrhea. To replace lost fluid, advise patients with no contraindication to increase intake by up to 3 to 4 litres per day. • Drink several types of fluid, including plain water and electrolyte-containing drinks, such as clear broth, gelatin desserts, sports drinks, flat soft drinks, or decaffeinated tea
Anal care[20]	Advise patients to: • Clean the anal area with mild soap and warm water after each bowel movement to prevent irritation • Apply a barrier cream or ointment, such as petroleum jelly or Isle's paste • Soak in a warm bathtub or sitz bath to relieve discomfort • Examine the anal area for red, scaly or broken skin
Diet[21]	Advise patients to: • Advise patients to eat and drink small quantities of food often • Avoid spicy, greasy, or fried foods • Follow the BRAT (banana, rice, applesauce, toast) diet, along with clear liquids, until diarrhea begins to resolve • Avoid cabbage, Brussels spouts, and broccoli, which may produce stomach gas, bloating and cramps

Key facts: Diarrhea

EGFR-induced diarrhea often has early warning signs. Early recognition and intervention may lead to a more favorable outcome.[22] Loperamide is recommended to treat moderate to severe diarrhea in patients treated with erlotinib and chemotherapy-induced diarrhea.[1,20,21]

Diarrhea may begin about 12 days after the start of EGFRI therapy. It is usually mild and does not worsen with time.1[9] Co-administration of the IV drug cetuximab with irinotecan or radiation therapy increases the likelihood and intensity of diarrhea.[3,8]

When patients seek OTC treatment for diarrhea, it is important to ask them about:[21]

- Number of stools per day and stool composition, e.g., watery, presence of blood, nocturnal
- Presence of diarrhea before their last treatment
- Medication profile to identify other agents that may contribute to diarrhea
- Dietary profile
- Signs and symptoms of complicated diarrhea, including:
  - Blood in stool
  - Dehydration, e.g., oral dryness, low urine production or dark yellow urine, weight loss, dry eyes or mouth, sunken eyes, low pulse, dizziness or feeling faint when getting up
  - Fever
  - Lethargy or altered mental state
  - Nausea and vomiting
  - Signs of infection
  - Stomach cramps

Eye disorders

Eye disorders occur in about one-third of patients treated with EGFR inhibitors.[23] These agents may cause eye and eyelid irritation, oily secretions and crustiness around the eyes; a grittiness, burning or foreign body sensation in the eye; eyelid growth; and some vision fluctuation.[22]

Dry eye[6,22,23]

Prevention	No preventive measures are recommended.	
Management	**OTC treatment** • Eye products with no preservatives such as lubricating eye drops, gels, gel inserts or ointments and artificial tears, 4 to 6 times daily • Warm eye soaks • Wear close-fitting glasses or sunglasses • Use a humidifier to moisten indoor air and change furnace air filters often	**Prescription medication** • Corticosteroid eye drops to decrease inflammation

Conjunctivitis[22,24]

Prevention	No preventive measures are recommended.
Management	• Ophthalmic antibiotic drops or ointments (OTC or prescription) • Topical steroid eye preparations

Key facts: Eye disorders

Among the most common side effects are conjunctivitis and keratoconjunctivitis sicca (dry eye).[1-4] Mild to moderate cases of both conditions usually respond to traditional OTC therapies.[22]

EGFRI-induced conjunctivitis differs from pink eye in that redness, itchiness, and swelling of the clear, thin, mucous membrane under the eyelid and covering the sclera (whites of the eye) is likely caused by an inflammatory reaction to targeted therapy rather than a bacterial or viral infection. However, a typical pink eye infection may occur as a result of EGFRI-induced dry eye. Conjunctivitis of infectious origin may resolve on its own within a week (viral) or respond to topical antibiotic therapy (bacterial).[22,23]

Refer immediately to eye doctor

Patients who report the following symptoms to contact an eye doctor immediately:[24]

- Unrelenting eye pain
- Loss of vision
- Extreme eye redness
- Light sensitivity
- No improvement in eye symptoms after 1 week of OTC therapy

Stomatitis

In patients treated with EGFR inhibitors, the integrity of mucous membranes in the mouth may be compromised, leading to inflammation.[6,17,25] This condition occurs from 8% to 23% of patients treated with an EGFR inhibitor alone and up to 26% in patients on combination therapy.[1-4] It may occur more frequently in patients treated with cetuximab and erlotinib.[1,3]

Prevention

Advise patients to:[19]

- Avoid cheek or lip biting
- Avoid mouth breathing
- Maintain good oral hygiene
- Maintain dentures by brushing daily and soaking in antimicrobial solution for at least 30 minutes/day and rinse thoroughly
- Avoid spicy and highly textured foods
- Avoid highly flavoured and alcohol-containing mouthwashes

Management

OTC treatment

For mild cases of mouth sores, pain, or redness on the inner cheeks, tongue, or lips

Meticulous oral hygiene:[25-27]

- Toothbrushing, 3-4 times daily with soft-bristle toothbrush. Soak toothbrush in warm water to soften bristles
- If brushing is painful, Toothettes (sponge-tipped stick with toothpaste), sponges, or gentle use of Waterpik®
- Biotene toothpaste is non-irritating contains natural salivary enzymes to control bacteria
- Floss gently once daily to avoid gum injury
- Salt and baking-soda rinses (1/2 teaspoon of each ingredient in 1 cup of warm water at least 4 times daily, especially after meals)
- Bland rinses, antimicrobial mouthwash
- OTC analgesics, such as ibuprofen (e.g., Advil®, Motrin®) and acetaminophen (e.g., Tylenol®)

Refer to doctor if patient has difficulty eating or drinking sufficient fluids or if redness is associated with lesions on the inner cheeks, tongue or lips[6]

Prescribed medication

(moderate to severe cases):

- Topical fluoride (dentist)[26]
- Topical anesthetics[26]
- Corticosteroid solution[6,25]
- Topical or systemic analgesics[26]
- Topical or systemic antifungals[25]
- Palliative mixtures of various agents[26]

Key facts: Stomatitis

Maintaining mucosal health, integrity, and function is crucial in patients with stomatitis. From 3 to 10 days after therapy begins, EGFRI-treated patients may experience a burning sensation, followed by mouth sores (ulcerations). Treatment aims to relieve symptoms until the mucous membranes can rejuvenate, usually within 7 to 14 days. Smokers have a greater risk of stomatitis.[25]

Clinical practice guidelines stress its importance in cancer patients, but due to a lack of supportive evidence, oral hygiene methods are usually based on personal preference and anecdotal experience.[26]

Good oral hygiene:[25,26]

- Reduces the severity of stomatitis
- Reduces mouth pain
- Reduces oral bleeding
- Reduces the risk of dental complications
- Minimizes the risk of soft tissue infections
- Enables patients to maintain a nutritious diet

The use of chlorhexidine mouth rinses is not recommended.

- They contain alcohol and may sting. Dilution defeats their antibacterial benefits.[25]

Hydrogen peroxide rinses may worsen mouth ulcers.[25]

There are no evidence-based guidelines for treatment of EGFRI-induced stomatitis, and practitioners usually follow the common practices for chemotherapy-induced mouth inflammation.

Topical preparations in widespread use for stomatitis contain ingredients such as lidocaine, benzocaine, milk of magnesia, kaolin, pectin, and dyphenhydramine. There is no significant evidence of the effectiveness or tolerability of these concoctions, and some may be only minimally better than saline rinses. Clinical trials in chemotherapy patients with stomatitis have shown no difference in the effectiveness of chlorhexidine mouthwash, "magic" mouthwashes that contain lidocaine, and salt-and-baking soda rinses.[26]

Xerostomia

Dry mouth occurs in about 6% of patients who take IV EGFR inhibitors, especially when combined with other cancer therapies, particularly radiation therapy.[1-4,28]

Prevention

Advise your patients:[27]

- Examine their mouth daily for red, white or dark patches, sores or signs of tooth decay
- Chew sugarless gum or candies to increase saliva flow
- Avoid alcohol-containing mouthwashes or dental products
- Use a cool-mist humidifier, especially at night
- Sip water throughout the day or suck on ice chips
- Modify your diet to drink 8 cups of water daily; eat soft, moist food; avoid alcohol, caffeinated beverages, and spicy, sugary, or acidic foods
- Avoid smoking

Management		
	OTC treatment Artificial saliva Meticulous oral hygiene:[27,28] • Toothbrushing, 2-4 times daily with soft-bristle toothbrush. Soak toothbrush in warm water to soften bristles • Floss gently once daily to avoid gum injury • Salt and baking-soda rinses (1/2 teaspoon of each ingredient in 1 cup of warm water at least 4 times daily, especially after meals) • Use a low-abrasive fluoride toothpaste • Avoid products that contain sodium lauryl sulfate, which may worsen canker sores • Orajel®, Vaseline® or glycerin swabs to relieve dryness and cracks on lips and under dentures	**Prescribed medications**[27,28] • Fluoride gel (dentist) • Drugs, such as pilocarpine, that increase saliva production

Key facts: Xerostomia

Like other chemotherapy drugs, EGFR inhibitors may damage the salivary glands, leading to xerostomia (dry mouth). This condition differs from stomatitis and is characterized by:[27]

- A dry, tough tongue
- Cracks in lips and at corners of mouth
- Pain or burning in mouth or on tongue
- Sticky, dry mouth
- Thick, stringy saliva

Patients may have difficulty speaking or swallowing, a constant sore throat, hoarseness, and dry nasal passages that lead to nosebleeds. Xerostomia can cause mouth sores, gum disease and tooth loss. One of the most common oral infections associated with xerostomia is oral candidiasis.[28]

References

1. TARCEVA® (erlotinib) product monograph. Hoffman-La Roche Ltd., January 9, 2009.
2. IRESSA® (gefitinib) product monograph. AstraZeneca Canada Inc. December 12, 2008.
3. ERBITUX® (cetuximab) product monograph. ImClone Systems Inc., March 4, 2009.
4. VECTIBIX® (panitumumab) product monograph. Amgen Manufacturing Ltd., March 5, 2009.
5. Ciardiello F, Tortora G. EGFR antagonists in cancer treatment. N Engl J Med 2008;358:1160-1174.
6. Morse L, Calarese P. EGFR-targeted therapy and related skin toxicity. Seminars in Oncology Nursing 2006;22(3):152-162.
7. Castillo L, Etienne-Grimaldi MC, Fischel JL, Formento N, et al. Pharmacological background of EGFR targeting. Annals of Oncology 2004;15:1007-1012.
8. Widakowich C, De Castro G, De Azambuja E, Dinh P, Awada A. Review: Side effects of approved targeted therapies in solid cancers. The Oncologist 2007;12:1443-1455.
9. Peréz-Soler R, Delord JP, Halper A, Kelly K, et al. HER1/EGFR inhibitor-associated rash: future directions for management and investigation outcomes from the HER1/EGFR inhibitor rash management forum. The Oncologist. 2005;10:345-356.
10. Managing side effects of EGFR inhibitors. Caring for Oncology Patients: Tips and Tools for managing targeted therapy. Little Falls, NJ; Projects in Knowledge Inc., 2009.
11. Lynch TJ, Kim ED, Eaby B, Garey J, et al. Epidermal growth factor receptor inhibitor-associated cutaneous toxicities: an evolving paradigm in clinical management. The Oncologist 2007;12:610-621.
12. Segaert S, Custem EV. Clinical signs, pathophysiology, and management of skin toxicity during therapy with epidermal growth factor inhibitors. Annals of Oncology 2005;16:1425-1433.
13. Wacker, B, Nagrani T, Weinberg J, Witt K, et al. Correlation between development of rash and efficacy in patients treated with the epidermal growth factor receptor tyrosine kinase erlotinib in two large phase III studies. Clinical Cancer Research 2007;13:3913-3921.
14. Melosky B, Burkes R, Rayson D, Alcindor T, et al. Management of skin rash during EGFR-targeted monoclonal antibody treatment for gastrointestinal malignancies: Canadian recommendations. Curr Oncol 2009;16:16-26.
15. Lacouture ME. Mechanisms of cutaneous toxicities to EGFR inhibitors. Cancer 2006;6:803-812.
16. Lacouture ME, Boerner SA, LoRusso PM. Non-rash skin toxicities associated with novel targeted therapies. Clinical Lung Cancer 2006;8(1):S36-S42.
17. Hu JC, Sadeghl P, Pinter-Brown LC, et al. Cutaneous side effects of epidermal growth factor receptor inhibitors: clinical presentation, pathogenesis, and management. J Am Acad Dermatol 2007;56:317-326.
18. Eaby B, Culkin A, Lacouture ME. An interdisciplinary consensus on managing skin reactions associated with human epidermal growth factor receptor inhibitors. Clin J Oncol Nurs 2008;12:283-290.
19. Regroupement des pharmaciens en oncologie. General information for patients. Protocol: Erlotinib. Conseil de lutte contre le cancer. APES. GEOQ. September 2005.
20. Richardson G, Dobish R. Chemotherapy-induced diarrhea. J Oncol Pharm Pract 2007; 13:181-198.

21. Saltz LB. Understanding and managing chemotherapy-induced diarrhea. Supportive Oncology 2003;1:35-46.
22. Basti S. Ocular toxicities of epidermal growth factor receptor inhibitors and their management. Cancer Nursing. 2007;30:S10-S16.
23. National Eye Institute. National Institutes of Health. Dry eye. March 3, 2009. Accessed at: www.nei.nih.gov.
24. Dunne M, Summer DK. EGFR inhibitors: toxicities and strategies for effective management. August 29, 2008. Accessed online at: www.medscape.com/viewprogram/17187_pnt.
25. Rosenbaum EH, Silverman S, Festa B, Rosenbaum I, et al. Mucositis: chemotherapy problems and solutions. Cancer Supportive Care Programs. October 2007. Accessed online at: www.cancersupportivecare.com/drug.php.
26. Rubenstein EB, Peterson DE, Schubert M, Keefe D, et al. Clinical practice guidelines for the prevention and treatment of cancer therapy-induced oral and gastrointestinal mucositis. Cancer. 2004;100(9) suppl:2026-2046.
27. Cancer.Net. Dry mouth or xerostomia. February 2009. Accessed at: www.asco.org
28. Bartels CL. Helping patients with dry mouth. Oral Cancer Foundation. Accessed at: www.oralcancerfoundation.org/dental/xerostomia.htm

Overview of HER2 inhibitors

This chapter contains information on the prevention and management of common side effects of human epidermal growth factor-2 (HER2) inhibitors that you are likely to encounter among cancer patients in your practice.

Two medications are available that inhibit the action of HER2.

- Lapatinib is an oral medication that is combined with certain chemotherapeutic agents to treat advanced HER2-positive breast cancer.[1]
- Trastuzumab is an intravenous infusion for patients with HER2-positive breast cancer.[2]

HER2 inhibitors

Lapatinib (Tykerb®)
Trastuzumab (Herceptin®)

There are few evidence-based guidelines on how to manage HER2 inhibitor-induced side effects. The recommendations presented here are based on a review of clinical practice guidelines, expert opinion, and best practices in oncology. For a complete description of all side effects, please consult the product monographs[1,2]

HER2 in cancer

Four receptors on cell membranes transmit growth signals into cells when activated by human epidermal growth factor (HER). This family of receptors is essential for normal cell development. They include:[1,3,4]

- HER1, also known as the epidermal growth factor receptor (EGFR)
- HER2, also known as HER2/neu
- HER3
- HER4

In 25% to 30% of breast cancers, the HER2 receptor is overexpressed on cell surfaces or in a state of continuous activation, flooding the cell with growth signals. In HER2-positive breast cancers, too many growth signals lead to:[3]

- Uncontrolled cell proliferation
- Higher potential for the invasion and spread of cancer
- Resistance to natural cell death (apoptosis)

HER2-positive breast cancer is likely to be aggressive and patients with this cancer have a higher risk of relapse and poorer prognosis than other breast-cancer patients.[2]

Drug administration

Lapatinib

- This medication is part of a dosing regimen that usually contains capecitabine. Patients take lapatinib orally once daily for 21 days as part of a repeating cycle that might include a twice-daily dose of capecitabine from Days 1 to 14.[1]

How to take lapatinib

- Take lapatinib on an empty stomach at least one hour before or two hours after a meal with a low fat content, as systemic exposure to lapatinib is increased when administered with food.[1,5]
- Take your pills all at once. Dividing the dose is not recommended. Do not crush, split or dissolve the tablets.[3]
- If you miss a dose, take it as soon as possible that day. Do not double your dose the next day.[1]
- Do not eat or drink grapefruit products, star fruit, or Seville oranges or take herbal medications, such as St. John's wort, while on lapatinib.[3,6]

Trastuzumab

- Trastuzumab is administered as an intravenous infusion in the hospital or clinic setting. The duration of treatment depends on the patient's stage of HER2-positive breast cancer.[2]

Mechanism of action

Lapatinib

- This medication is a small molecule tyrosine kinase (TK) inhibitor that crosses the cell membrane to work inside cancer cells. It targets the intracellular portion of EGFR and HER2 receptors in order to prevent the transmission of biochemical signals within cells that promote cancer-cell growth and proliferation.[1,3,4,7]

Trastuzumab

- This medication is a monoclonal antibody that works outside cancer cells. It targets the extracellular portion of HER2 receptors to stop the transmission of growth signals into cells.[2]

By interrupting growth signal transmission, HER2 inhibitors:[1,2,8]

- Stop cancer-cell growth and proliferation
- Restore apoptosis (natural cell death)

Basic pharmacokinetics

Lapatinib is metabolized in the liver via the CYP3A4 and CYP2C8 pathways. It will interact with strong inducers or inhibitors of these pathways, causing significant changes in plasma concentrations of lapatinib within the body.[1] For example, carbamazepine can reduce systemic exposure to lapatinib by about 72%, while ketoconazole can boost it about 3.6-fold.[1]

Because lapatinib inhibits P-glycoprotein (PGP), it will alter the plasma levels of drugs that are PGP substrates. When taken with PGP inhibitors, such as cyclosporine or nifedipine, plasma levels of lapatinib will increase.[1] This medication can prolong the QT interval and should be used with caution in patients on high-dose anthracycline therapy, patients with hypokalemia, hypomagnesemia or congenital long QT syndrome, and patients who use anti-arrhythmic medications or other medicines that lead to QT prolongation.[1]

There are no know drug-drug interactions with trastuzumab; however, the use of combination therapy with anthracyclines is contraindicated due to the higher risk of side effects.[2]

Prevention and management of common side effects

The following table summarizes the most common side effects of HER2 inhibitors.[1] The side-effect profiles of lapatinib and trastuzumab differ, primarily because trastuzumab blocks HER2, while lapatinib blocks EGFR and HER2.[1,2]

Common side effects of HER2 inhibitors

Click on side effects highlighted in blue for more information and click on the arrow to return.

Trastuzumab

Cardiovascular disorders
- Peripheral edema

Gastrointestinal disorders
- Constipation
- **Diarrhea**
- Nausea
- **Stomatitis**
- Vomiting

General disorders
- Anorexia
- Anxiety
- Dizziness
- Fatigue
- Headache
- Insomnia
- Pain (abdominal, chest and other pain)
- Weakness

Musculoskeletal and connective tissue disorders
- Back pain
- Pain in extremities
- Respiratory disorders
- Cough
- Dyspnea

Skin disorders
- **Rash**, pruritis

Lapatinib

Gastrointestinal disorders
- **Diarrhea**
- Dyspepsia
- Loss of appetite
- Nausea
- **Stomatitis**
- Vomiting

General disorders
- Fatigue
- Insomnia
- Mucosal inflammation

Musculoskeletal and connective tissue disorders
- Back pain
- Pain in extremities
- Respiratory disorders
- Dyspnea

Skin disorders
- Hand-foot skin reactions
- **Rash**
- Xerosis

Infusion reactions, associated with trastuzumab, include chills, fever, or tachycardia. They are usually encountered in the clinic or hospital setting and will not be discussed here.

HER2 inhibitors are often combined with other anticancer medications. These combination regimens may give rise to side effects that are not associated with HER2 inhibitors but are attributable to another medication in the therapeutic regimen. A prime example is hand-foot skin reaction, also known as hand-foot syndrome and palmar-plantar erythrodysesthesia.[1,9] It occurs in 53% of patients on lapatinib-capecitabine therapy but <1% of patients taking lapatinib alone.[1,9]

Refer for medical attention

- Patients with the following symptoms should contact their doctor:
- 4 extra bowel movements per day or night-time diarrhea.[2]
- Shortness of breath, which may signal heart problems in women with water retention in the lower legs, anemia in women with dizziness, a racing heart, or lightheadedness, or lung problems in women with a persistent wheeze or cough.[2]
- Signs of infection (fever, chills, sore throat, redness, pain), as infection may be a sign of a reduced white blood cell count.[2]
- An abnormal heartbeat, which may signal a heart problem, such as left ventricular dysfunction or congestive heart failure, a less common but potentially serious side effects of trastuzumab.[4]
- Severe liver damage (itching, yellow eyes or skin, dark urine, tiredness, or pain in the upper right belly), a rare but potentially life-threatening side effect of lapatinib. Symptoms can occur within days or several months after initiation of treatment.[1,3]

Rash

Skin rash occurs in up to 43% of patients on lapatinib therapy.[9] Rash is a common side effect of medications that block the HER1 (EGFR) receptor, including lapatinib.[10] Some evidence suggests that the early introduction of preventive strategies may reduce the severity of skin reactions.[18] Prevention and treatment are based on clinical experience with EGFR-induced rash, even though lapatinib-related rash differs from the latter in both frequency and severity.[3,4,9,10,12]

Prevention

A proactive approach is critical in managing rash.[10] When patients begin therapy, advise them to:[4,9,12]

- Cleanse with mild soaps or cleaners or bath or shower oils to avoid skin dryness.
- Moisturize twice a day with thick, emollient-based creams, such as Aveeno® lotion, Neutrogena® Norwegian Formula hand cream, or Vaseline Intensive Care® Advanced Healing Lotion.
- Use only fragrance- , alcohol-, and dye-free lotions and cosmetics.
- Use a dermatologist-approved cover-up, such as Dermablend® or Cover FX®, to conceal the rash.
- Remove make-up with a gentle, skin-friendly cleanser, e.g., Neutrogena®, Dove®
- Use a broad-spectrum sunscreen (SPF 15 or greater) that contains zinc oxide or titanium dioxide.

Management			
	Mild[4,10,12] • Localized • Reddish skin spots or bumps without other symptoms • No impact on daily activities • No sign of infection	No treatment or: • Topical hydrocortisone 0.5% cream[12] **Advise patient to monitor the rash for changes in severity.**[1,2] **Refer to doctor if rash persists after 2 weeks of treatment or worsens in severity.**[10]	**Prescribed medications** Topical agents with anti-inflammatory properties, such as hydrocortisone 1% to 2.5% cream, metronidazole cream or clindamycin 1% gel,[12]
	Moderate[4,10,12] • Localized skin peeling or sloughing • Reddish skin spots or bumps with other symptoms, e.g., redness, itchiness, burning, swelling, or tenderness • Lesions cover <50% of body surface • Minimal impact on daily activities **Refer to doctor.**	**Advise patient to monitor the rash for changes in severity.**[1,2] **Advise patient to consult doctor if symptoms persist or worsen after 2 weeks of treatment.**[12]	**Prescribed medications**[10,12] • Topical corticosteroid, such as hydrocortisone 2.5% cream, clindamycin 1% gel or pimecrolimus 1% cream PLUS • doxycycline (100-mg BID) or minocycline (100-mg BID)

Key facts: Rash

Most lapatinib-related rashes are:[9,10]

- mild to moderate in severity
- develop early in treatment
- inflammatory rather than infectious in nature

Unlike EGFR-induced rash, lapatinib-related skin rashes usually appear on the trunk and infrequently on the face. Pruritis is rare. The rash usually resolves during treatment, after a temporary interruption of treatment, or when therapy ends.[10] There is no evidence that skin rash may signal a positive response to lapatinib in patients with breast cancer.[10]

To determine the best strategy for managing rash, it is important to ask patients if they have other symptoms. The presence of other symptoms may indicate a need to refer patients to a doctor or dermatologist for treatment. These symptoms include:[4]

- Burning
- Edema
- Itchiness
- Redness
- Tender skin

Diarrhea

There are no evidence-based guidelines for the management of diarrhea in patients who take HER2 inhibitors.[10] Recommendations are generally based on those for chemotherapy-induced diarrhea.[10] Dietary modifications are not recommended in anticipation of diarrhea.[13]

Prevention	No prevention measures are recommended.
Management OCT therapy[10,13,14] **Refer to doctor if moderate diarrhea does not improve after 24 hours of treatment**	Aggressive use of loperamide (e.g., Imodium®) for early-onset diarrhea **Mild to moderate (less than 4 loose stools per day)** • Follow instructions on package insert: 2 tablets immediately, then 1 tablet after each liquid bowel movement (maximum: 8 tablets/24 hours) **Moderate (more than 4 to 6 loose stools per day or night-time diarrhea)** • 2 tablets immediately, then 1 tablet every 2 hours during the day and 2 tablets every 4 hours during the night until bowel movements are normal for at least 12 hours • **This dosage is higher than packaging recommendations. Advise your patients that it is important to take the medication at higher doses to stop diarrhea**
Replace lost fluids[3,10,13,14]	• Fluid intake is more critical than food intake in patients with diarrhea. To replace lost fluid, advise patients with no contraindication to increase intake by up to 3 to 4 litres per day. • Drink several types of fluid, including plain water and electrolyte-containing drinks, such as clear broth, gelatin desserts, sports drinks, flat soft drinks, or decaffeinated tea
Anal care[13]	Advise patients to: • Clean the anal area with mild soap and warm water after each bowel movement to prevent irritation • Apply a barrier cream or ointment, such as petroleum jelly or Isle's paste • Soak in a warm bathtub or sitz bath to relieve discomfort • Examine the anal area for red, scaly or broken skin
Diet[4,14]	Advise patients to: • Advise patients to eat and drink small quantities of food often • Avoid spicy, greasy, or fried foods • Follow the BRAT (banana, rice, applesauce, toast) diet, along with clear liquids, until diarrhea begins to resolve • Avoid cabbage, Brussels spouts, and broccoli, which may produce stomach gas, bloating and cramps

Key facts: Diarrhea

Diarrhea occurs in 65% of patients taking lapatinib and capecitabine, and in about 27% of patients taking trastuzumab for advanced breast cancer.[1,2] Diarrhea is the most common reason that patients stop taking lapatinib in clinical trials.[15]

When patients seek OTC treatment for diarrhea, it is important to ask them about:[4,14,15]

- Number of stools per day and stool composition, e.g., watery, presence of blood, nocturnal
- Presence of diarrhea before their last treatment
- Medication profile to identify other agents that may contribute to diarrhea
- Dietary profile
- Signs and symptoms of complicated diarrhea, including:
  - Blood in stool
  - Dehydration, e.g., oral dryness, low urine production or dark yellow urine, weight loss, dry eyes or mouth, sunken eyes, low pulse, dizziness or feeling faint when getting up
  - Fever
  - Lethargy or altered mental state
  - Nausea and vomiting
  - Signs of infection
  - Stomach cramps

When to refer

Almost 3 in 20 patients (14%) taking lapatinib and capecitabine develop severe diarrhea. Urge these patients to consult their doctor for treatment if:[4,13,15]

- They do not respond to loperamide after >24 hours
- Fever is present

Stomatitis

Stomatitis (mouth sores) occurs in about 14% of patients taking lapatinib. The incidence of stomatitis is much lower (≤4%) in patients taking trastuzumab.[1]

Prevention

Advise patients to:[16,17]

- Avoid cheek or lip biting
- Avoid mouth breathing
- Maintain god oral hygiene
- Maintain dentures by brushing daily and soaking in antimicrobial solution for at least 30 minutes/day and rinse thoroughly
- Avoid spicy and highly textured foods
- Avoid highly flavoured and alcohol-containing mouthwashes

Management

OTC treatment

For mild cases of mouth sores, pain, or redness on the inner cheeks, tongue, or lips

Meticulous oral hygiene:[16,17]

- Toothbrushing, 3-4 times daily with soft-bristle toothbrush. Soak toothbrush in warm water to soften bristles
- If brushing is painful, Toothettes (sponge-tipped stick with toothpaste), sponges, or gentle use of Waterpik®
- Biotene toothpaste is non-irritating contains natural salivary enzymes to control bacteria
- Floss gently once daily to avoid gum injury
- Salt and baking-soda rinses (1/2 teaspoon of each ingredient in 1 cup of warm water at least 4 times daily, especially after meals)
- Bland rinses, antimicrobial mouthwash
- OTC analgesics, such as ibuprofen (e.g., Advil®, Motrin®) and acetaminophen (e.g., Tylenol®)

Refer to doctor if patient has difficulty eating or drinking sufficient fluids or if redness is associated with lesions on the inner cheeks, tongue or lips[15]

Prescribed medication

(moderate to severe cases):[16,17]

- Topical fluoride (dentist)
- Topical anesthetics
- Corticosteroid solution
- Topical or systemic analgesics
- Topical or systemic antifungals
- Palliative mixtures of various agents

Key facts: Stomatitis

Lapatinib-induced stomatitis may be related to its effects on EGFR, as stomatitis is a common side effect of EGFR inhibitors.[16,17] There are no evidence-base strategies for its management. Maintaining mucosal health, integrity, and function is crucial in patients with stomatitis. Treatment aims to relieve symptoms until the mucous membranes can rejuvenate themselves, usually within 7 to 14 days. Smokers have a greater risk of stomatitis.[17]

Clinical practice guidelines stress the importance of oral hygiene in cancer patients, but due to a lack of supportive evidence, the methods are usually based on personal preference and anecdotal experience.[16]

Good oral hygiene:[16,17]

- Reduces the severity of stomatitis
- Reduces mouth pain
- Reduces oral bleeding
- Reduces the risk of dental complications
- Minimizes the risk of soft tissue infections
- Enables patients to maintain a nutritious diet

The use of chlorhexidine mouth rinses is not recommended.

- They contain alcohol and may sting. Dilution defeats their antibacterial benefits.[17]

Hydrogen peroxide rinses may worsen mouth ulcers.[17]

There are no evidence-based guidelines for treatment of EGFRI-induced stomatitis, and practitioners usually follow the common practices for chemotherapy-induced dry mouth.

Topical preparations in widespread use for stomatitis contain ingredients such as lidocaine, benzocaine, milk of magnesia, kaolin, pectin, and diphenhydramine. There is no significant evidence of the effectiveness or tolerability of these concoctions, and some may be only minimally better than saline rinses. Clinical trials in chemotherapy patients with stomatitis have shown no difference in the effectiveness of chlorhexidine mouthwash, "magic" mouthwashes that contain lidocaine, and salt-and-baking soda rinses.[16]

References

1. Tyberk product monograph (USA). GlaxoKlineSmith USA, July 2008.
2. Herceptin product monograph. Hoffman-La Roch Ltd., November 4, 2008.
3. Your patients want more. A treatment guide to using Tykerb. GlaxoKlineSmith Oncology; USA. July 2008.
4. More options surround me. Your treatment with Tykerb. GlaxoKlineSmith Oncology; USA. July 2008.
5. Koch KM, Reddy NJ, Cohen RB, Lewis NL, et al. Effects of food on the relative bioavailability of lapatinib in cancer patients. J Clin Oncol 2009;10:1191-1196.
6. American Society of Health-System Pharmacists. Lapatinib. AHFS Consumer Medication Information. September 2007. Accessed online at: www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=meds&part=a607055.
7. Paul B, Trovato JA, Thompson J. Lapatinib: a dual tyrosine kinase inhibitor for metastatic breast cancer. Am J Health Syst Pharm 2008;65:1703-1710.
8. Widakowich C, De Castro G, De Azambuja E, Dinh P, Awada A. Review: Side effects of approved targeted therapies in solid cancers. The Oncologist 2007;12:1443-1455.
9. Lacouture, ME, Laabs SM, Koehler M, Sweetman RW, et al. Analysis of dermatologic events in patients with cancer treated with lapatinib. Breast Cancer 2009;114:485-493.
10. Moy B, Goss PE. Lapatinib-associated toxicity and practical management recommendations. The Oncologist 2007;12:756-765.
11. Melosky B, Burkes R, Rayson D, Alcindor T, et al. Management of skin rash during EGFR-targeted monoclonal antibody treatment for gastrointestinal malignancies: Canadian recommendations. Curr Oncol 2009;16:16-26.
12. Lynch TJ, Kim ED, Eaby B, Garey J, et al. Epidermal growth factor receptor inhibitor-associated cutaneous toxicities: an evolving paradigm in clinical management. The Oncologist 2007;12:610-621.
13. Richardson G, Dobish R. Chemotherapy-induced diarrhea. J Oncol Pharm Pract 2007;13:181-198.
14. Saltz LB. Understanding and managing chemotherapy-induced diarrhea. Supportive Oncology 2003;1:35-46.
15. Managing side effects of HER2 inhibitors. Caring for Oncology Patients: Tips and Tools for managing targeted therapy. Little Falls, NJ; Projects in Knowledge Inc., 2009.
16. Rubenstein EB, Peterson DE, Schubert M, Keefe D, et al. Clinical practice guidelines for the prevention and treatment of cancer therapy-induced oral and gastrointestinal mucositis. Cancer. 2004;100(9) suppl:2026-2046.
17. Rosenbaum EH, Silverman S, Festa B, Rosenbaum I, et al. Mucositis: chemotherapy problems and solutions. Cancer Supportive Care Programs. October 2007. Accessed online at: www.cancersupportivecare.com/drug.php.

Overview of Multi-targeted kinase inhibitors

This chapter contains information on the prevention and management of common side effects of multi-targeted kinase inhibitors (MKIs) that you are likely to encounter among cancer patients in your practice.

There are no evidence-based guidelines on how to manage MKI-induced side effects. The recommendations presented here are based on a review of expert opinion and best practices in oncology. For a complete description of all side effects of these agents, please consult the product monographs.[1,2]

MKIs

Sorafenib (Nexavar®)
Sunitinib (Sutent®)

Several medications are available that inhibit the action of multiple tyrosine kinases (TKs).[1-3] They target different TKs; hence, their side-effect profiles vary.[1-3] This chapter will focus on two oral medications that target multiple cell signaling pathways to treat gastrointestinal, kidney, or liver cancers. For information on targeted therapy for GIST, see c-Kit inhibitors.

Multiple TKs in cancer

Tyrosine kinases (TKs) are essential for normal cell signaling. These enzymes regulate cell proliferation, survival, differentiation, function, and motility.[1-3] They fall into two main classes:[3]

- Receptor TKs are an integral part of receptors that traverse the cell membrane. Targeted TKs may be located on receptor sites outside or inside the cell.
- TKs (non-receptor TKs) are found in the cytosol, nucleus, or inner surface of cells.

In cancer cells, the normal regulatory activity of TKs can be disrupted in three ways:[3]

- The cell produces too many normal TK receptors, their ligands, or both
- A local mutation permanently "switches on" the TK receptor
- DNA mutations create oncoproteins that bind to TKs or TK receptors

Whatever the cause of TK dysregulation, the result is the same. The TK or TK receptor is continuously activated. It transmits a constant stream of signals into cancer cells, promoting cell growth and proliferation, inhibiting apoptosis, and enhancing cell motility, which leads to the spread of cancer.[3]

Drug administration

Sunitinib

- This medication is taken once daily – with or without food. It is administered on a 4-week on treatment, 2-week off treatment schedule.[1]

Patients who take MKIs should avoid grapefruit juice.[1,2]

Sorafenib

- Sorafenib is taken twice daily with a glass of water and without food or with low-fat to moderate-fat meals. With a high-fat meal, the bioavailability of sorafenib is 29% lower than when it is taken without food.[2]

Patients who miss a dose of either medication should not take a double dose on the next day to make up for it.[1,2]

Mechanism of action

Multi-targeted kinase inhibitors (MKIs) are small molecules that directly inhibit the activity of tyrosine kinases (TKs). They bind to TKs to prevent ATP or other substances from interacting with these enzymes, shutting down the biochemical transmission of cell signals. Different MKIs target different TKs and receptor TKs.[3]

Sunitinib

This medication targets different signaling pathways to block the activity of a number of TKs that are implicated in tumour growth and spread. One pathway is activated by vascular endothelial growth factor (VEGF). This pathway plays a critical role in the proliferation, migration, and survival of cells that grow new blood vessels (angiogenesis). In cancer, dysregulation of the VEGF pathway "switches on" angiogenesis, leading to new blood-vessel formation within and near tumours. Sunitinib inhibits the TKs of VEGF, disrupting the growth of new blood vessels that feed tumours.[2,4]

Sunitinib targets a second signaling pathway that is vital for angiogenesis. This pathway is mediated by platelet-derived growth factor (PDGF), which contributes to the stability and maturity of blood vessels. Dysregulation of this pathway leads to tumour growth and proliferation. By blocking PDGF TKs, sunitinib disrupts the stability and maturation of existing blood vessels that feed tumours.[2,4]

Sunitinib also blocks the activity of stem cell factor receptors (Kit), FMS-like TK-3 (FLT3), colony stimulating factor receptor (SCF-1R), and neurotrophic factor receptor (RET). By targeting multiple receptor TKs to disrupt abnormal cell signaling, sunitinib inhibits the:[2,4]

- Growth and proliferation of cancer cells
- New blood-vessel growth in and near tumours
- Migration of cancer cells

Sorafenib

Sorafenib also targets a number of TKs and receptor TKs that are implicated in tumour cell signaling, angiogenesis, and cell death. The most important of these pathways are VEGF and PDGF, which play crucial roles in angiogenesis. By blocking TKs on VEGF and PDGF receptors, sorafenib disrupts the abnormal signaling activity that switches on angiogenesis. This MKI also blocks abnormal signaling activity along the Raf-kinase, Kit, and RET pathways.[1,4]

By targeting multiple TKs, sorafenib inhibits the:[1,4]

- Growth and proliferation of tumours
- Tumour angiogenesis
- Survival of cancer cells

Basic pharmacokinetics

Sorafenib and sunitinib are metabolized primarily via the CYP3A4 pathway in the liver.[1,2] These MKIs interact with a host of CYP3A4 inducers, inhibitors, and substrates.[1,2] Sorafenib is a minor inhibitor of other metabolic pathways, including UGT1A9, CYP2C9, 2C19, and 2D6.[1,2]

Sunitinib can prolong the QT interval and PR interval, and decrease heart rate. Patients who take drugs with dsyrhythmic potential or drugs that prolong the PR interval, including beta-blockers, calcium channel blockers, digitalis, or HIV protease inhibitors, must use caution when taking sunitinib.[2]

Prevention and management of common side effects

Skin or hair colour changes

Skin or hair colour changes, particularly a yellowing or complete loss of color, can occur after the first week of sunitinib. Assure your patients that this side effect is reversible when therapy ends.[5]

Most patients who are treated with MKIs have side effects.[3] Patients with different cancers and different stages of cancer may react differently to the same MKI, mainly because their dosages may differ.[1-3]

Hand-foot skin reaction is very common in patients taking sunitinib and sorafenib.[1-3] The following table summarizes very common and common side effects of each medication.[1,2]

Thyroid function

Sunitinib can affect thyroid function as early as 2 weeks after its initiation. Advise your patient to see their oncologist for thyroid function testing if they experience any of these symptoms[6]

- Anorexia
- Cold intolerance
- Fatigue
- Swelling or fluid retention

Common side effects of multi-targeted kinase inhibitors

Click on side effects highlighted in blue for more information and click on the arrow to return.

Sorafenib

Very common

Bleeding disorders
- Bleeding from mouth, nose, stomach or gut, rectum, lungs or windpipe, nailbeds, blood blisters)

Cardiovascular disorders
- **Hypertension**

Gastrointestinal disorders
- **Diarrhea**, nausea, vomiting, constipation, loss of appetite, loss of weight, **stomatitis**

General disorders
- Fatigue, weakness
- Pain (abdominal pain, headache; joint, bone or muscle pain)

Respiratory disorders
- Breathlessness

Skin disorders
- Hair loss
- **Hand-foot skin reaction**, **rash**; **pruritis**; inflamed, dry, or scaly skin that sheds

Common

Cardiovascular disorders
- Flushing, heart attack

General disorders
- Flu-like illness, fever, depression, hoarseness, impotence

Gastrointestinal disorders
- Indigestion, heartburn, difficulty swallowing, infection or inflammation of gallbladder or bile ducts

Kidney disorders
- Kidney failure

Skin disorders
- Acne

Sunitinib

Very common

Blood disorders
- Low white blood cell and platelet counts

Cardiovascular disorders
- **Hypertension**

Gastrointestinal disorders
- Mouth pain or irritation, **stomatitis**, taste disturbances, upset stomach, nausea, vomiting, **diarrhea**, constipation, loss of appetite

General disorders
- Fatigue, headache

Skin disorders
- **Hand-foot skin reaction**, **rash**, skin discolouration, hair-colour change

Common

Bleeding disorders
- Nose bleed

Cardiovascular disorders
- Swelling

Gastrointestinal disorders
- Abdominal pain

General disorders
- Dizziness, weakness

Infection

Skin disorders
- Dry skin

Refer for medical attention: sunitinib

Refer patients with any of the following constellations (groupings) of symptoms to their doctor immediately:[2]

- Bleeding problems (blood in urine or stool; nose bleeds) and infection
- Blood clots (severe pain, swelling, or redness in legs or severe chest pain with shortness of breath)
- Heart problems (shortness of breath, fatigue, swollen feet and ankles)
- Low thyroid function (fatigue, constipation, dry skin, weight gain)
- Low white blood cell count (Infection, fever, bleeding)
- Myopathy or rhabdomyolysis (muscle aches or weakness, dark urine)
- Pancreatitis (abdominal pain, fever, nausea, vomiting)

When to stop sunitinib

Tell patients with rapid, pounding, or irregular heartbeat, dizziness, fainting, or seizures to stop taking sunitinib and seek emergency care.[2]

Refer for medical attention: sorafenib

Refer patients to a doctor if any of the following common side effects become severe:[1]

- Diarrhea, nausea, or vomiting
- Fatigue
- Fever
- Heartburn
- Inflamed, dry, scaly skin
- Joint or muscle pain
- Numbness or tingling
- Rash with itchiness, redness, or hives
- Stomatitis
- Weight loss

Tell patients to see their doctor if any of these common side effects occur, regardless of severity:[1]

- Bleeding from the mouth, nailbeds, or nose, in stool, sputum, or urine
- Breathlessness
- Hand foot skin reaction
- Hypertension

Tell patients to seek emergency care if any uncommon side effect occurs:[1]

- Dehydration
- Heart attack
- Multiple skin eruptions
- Severe eczema
- Severe stomach pain
- Severe, persistent runny nose
- Yellowing of skin or eyes (signs of jaundice)

Hand-foot skin reaction (HFSR)

From 30% to 60% of patients taking sorafenib and 15% to 20% of patients taking sunitinib develop hand-foot skin reaction (HFSR), also known as hand-foot syndrome and palmar-plantar erythrodysesthesia. HFSR is the most clinically significant, dose-limiting, skin-related side effect of MKIs.[7-11]

Prevention

During the first 2–4 weeks of therapy, prevention of traumatic activity and rest are crucial.[8] Urge your patients to:[8,10]

- Have a manicure or pedicure to remove thickened skin or calluses; follow with moisturizing cream
- Use a moisturizing cream
- Wear loose-fitting, soft shoes or slippers, foam absorbing soles, gel inserts to cushion pressure points, cotton socks
- Cushion callused areas with soft or padded shoes
- Reduce exposure of hands and feet to hot water (showers, dishwashing, etc.)
- Avoid excessive friction to hands or feet when performing tasks
- Avoid vigorous exercise or activities that place undue stress on the hands and feet
- Wear thick cotton gloves or socks to protect hands and feet and keep them dry
- Report any signs or symptoms of HFSR immediately to ensure early-stage treatment

Management

OTC treatment

Grade 1 (Mild; Discomfort, no disruption of activities)[8]

Advise patients to add the following:[8,10,11]

- Avoid hot water; cool water or cold compresses may ease symptoms
- Diligently apply moisturizers to keep palms and soles soft and pliable to prevent cracks or breaks in skin integrity
  - Use moisturizing creams twice daily
  - Use aloe vera lotion
  - Use 20% to 40% urea cream or 6% salicylic acid on callused areas
- Soak feet in magnesium sulfate (Epsom salts) to soften calluses and reduce pain on pressure
- Use low to moderate dose pain killers

Advise patients to consult their doctor about reducing their dosage of MKI, if symptoms of HFSR worsen after being treated for 2 weeks[8]

Prescribed therapy

Grade 2 (Moderate; Disrupts daily activity)[8]
Add the following:[8]

- Topical corticosteroid (e.g., clobetasol 0.05% ointment)
- 2% lidocaine topical ointment
- Oral NSAIDS, codeine, pregabalin, for pain
- Dose modification is required
- If symptoms worsen after 2 weeks, treatment interruption may be required

Grade 3 (Severe)[8]

- Treat as Grade 2
- Further dose modification is required
- If symptoms worsen after 2 weeks, treatment interruption may be required

For thick, tender sores after acute rash with/without blisters resolves:[8]

- 40% urea cream
- Tazarotene 0.1% cream
- Fluorouracil 5% cream

Key facts: HFSR

HFSR has a serious impact on the physical, psychological, and social well-being of patients who receive MKIs.[7-10] Treatment may require dosage adjustment or the interruption of life-prolonging therapy in cancer patients.[8,10] **The look and onset of this reaction is different than capecitabine-induced HFSR.** The typical pattern of localized sensitive lesions with skin thickening, surrounded by redness, differs from classic HFSR, in which symmetrical changes in skin sensation, redness and swelling occurs.[10]

Most cases of HFSR are mild to moderate, but about 5% to 6% of patients develop a severe reaction that impairs daily-living activities.[7-10] These patients may experience extreme tenderness of the hands and feet – enough to affect hand or foot function and disrupt their quality of life.[7] Patients taking sorafenib are 6.6 times more likely and patients taking sunitinib are 9.9 times more likely to develop HFSR than others.[8]

HFSR usually occurs within the first 2 to 4 weeks of MKI therapy.[8] Tender, scaly sores – with or without blistering – appear on the palms and soles. The edges of thickened skin patches on fingertips, toes, and other pressure or flexure points, such as elbows or knuckles, may be surrounded by a swollen, reddish halo.[7,8,11] The hands or feet may tingle or feel sensitive to touch or heat.[11]

After several weeks, thickened, callus-like skin skin develops over the sores. These areas are usually painful and impair range of motion, function, and weight bearing.[8]

There are no evidence-based guidelines for the management of MKI-related HFSR. Experts recommend prevention, early detection, and immediate treatment as crucial steps in the management of HSFR to prevent the withdrawal of life-prolonging MKI therapy.[10] The management of moderate to severe HFSR requires dose modification and a temporary interruption of MKI therapy until symptoms resolve. The patient's doctor may then reintroduce the MKI at a low dose and slowly escalate the dose to achieve therapeutic benefits without triggering a recurrence of HSFR.[10]

Skin products in use for HFSR[10]

- Cetaphil® skin cleansers
- Aveeno® shower gel
- Udderly Smooth®, Gold Bond®, Aveeno® lotions
- Norwegian Formula moisturizer and foot cream (Neutrogena®)
- Bag Balm®
- Eucerin® cream and Dry Skin Therapy
- Aquaphor® Healing Ointment
- Kerasal®
- Sunblock
- Lipikar, Lipikar balm, and Xerand

Hypertension

The incidence of high blood pressure (hypertension) varies among MKIs and in patients with different cancers.[1,2] Patients taking sorafenib are at least 6 times more likely to develop hypertension than others.[6,12] In patients on sunitinib, hypertension developed in 28% of those with kidney cancer and 15% of those with GIST.[12]

Monitoring	Encourage patients to: • Monitor their blood pressure (BP) weekly for the first 6 weeks of treatment then on a regular basis[6] • Keep a diary of blood-pressure readings[4]	
Management	Advise patients with uncontrolled hypertension to see their doctor immediately for treatment.[1,6]	**Prescribed therapy** • Most hypertension can be managed with standard antihypertensive therapy, taking into account possible drug interactions.[1,2,4,6] • Discontinuation of MKI therapy for severe hypertension or persistent hypertension despite treatment[1,2]

Key facts: Hypertension

Like other anti-angiogenic agents that inhibit VEGF, both sunitinib and sorafenib may cause a significant and sustained increase in blood pressure (BP).[12] Patients who receive these medications should be monitored for the onset or worsening of hypertension.[1,2]

Hypertension may develop in the first few weeks of therapy or slowly over time. Patients with MKI-induced hypertension may also develop proteinuria and should be screened for this side effect.[4,12]

Hypertension is usually mild to moderate and manageable with standard antihypertensive therapy. From 4% to 10% of patients develop moderately severe or severe hypertension.[6] Lifestyle modification is recommended for all patients with hypertension.[4,6,12]

Rash

Rash is a common side effect of sorafenib and sunitinib, occurring in up to 19% of patients.[1,2,5]

Prevention

A proactive approach is critical in managing rash. When patients begin therapy, advise them to:[13-15]

- Cleanse with mild soaps or cleaners or bath or shower oils to avoid skin dryness.
- Moisturize twice a day with thick, emollient-based creams, such as Aveeno® lotion, Neutrogena® Norwegian Formula hand cream, or Vaseline Intensive Care® Advanced Healing Lotion.
- Use only fragrance- , alcohol-, and dye-free lotions and cosmetics.
- Use a dermatologist-approved cover-up, such as Dermablend® or Cover FX®, to conceal the rash.
- Remove make-up with a gentle, skin-friendly cleanser, e.g., Neutrogena®, Dove®
- Use a broad-spectrum sunscreen (SPF 15 or greater) that contains zinc oxide or titanium dioxide.

Management

OTC therapy

Mild to moderate rash[16-18]

- Antihistamine (diphenhydramine)
- Topical steroid (hydrocortisone 0.5%)
- Coal tar preparations

Prescribed therapy

Moderate to severe rash[5,16]

- Topical corticosteroids (e.g., hydrocortisone 2.5%)
- Oral corticosteroids (e.g., prednisone 1 mg/kg daily with or without topical triamcinolone acetonide 0.1% ointment[13]
- Topical clindamycin 1%[5]

Key facts: Rash

Rash symptoms may occur after 6 weeks of sorafenib and 3 to 4 weeks of sunitinib.[6] This rash is similar to EGFR-induced rashes – albeit less frequent and milder – with spots and bumps on the upper chest, back or face that may or may not contain sterile fluid.[5] Generalized skin rashes are usually mild to moderate, tend to decrease over time, and rarely require dose reduction.[5,6]

Patients taking sorafenib may develop a reddish rash with scaly patches on the face and scalp from 1 to 2 weeks after treatment begins. This rash resembles acne but is inflammatory rather than bacterial in nature. It may be associated with a loss or distortion of sensation on the scalp. This rash generally fades or disappears after several weeks and prescribed therapy is not usually necessary.[12]

There are no evidence-based guidelines for the treatment of MKI-induced rash. Early recognition of symptoms and a prompt start of symptomatic therapy are the mainstays of treatment. Mild to moderate symptoms are managed while the patient remains on therapy. Refer any patient who develops a severe rash while taking MKIs to a doctor for evaluation and treatment.[5]

Pruritis

Pruritis (itchiness) is a common side effect of sorafenib.[2]

Prevention	To prevent dry skin, a common cause of itchiness, advise your patients to:[4] • Use mild soaps that contain no deodorants or fragrance, such as Dove® or Neutrogena® • Frequently apply lotions or bland emollients, such as Eucerin® cream, Neutrogena® Norwegian Formula Hand Cream, or Vaseline Intensive Care® Advanced Healing Lotion • Choose "anti-itch" products • Use liquid shower gels instead of soap	
Management	Mild to moderate pruritis Advise patients to:[4] • Apply more lotion than usual to help reduce or eliminate itchiness on the trunk or extremities • Use lotions with aloe vera or dimethicone Moisturel® • Use antidandruff shampoos and conditioners • Use hair products that contain tea tree oil, which contain extra moisturizers and may relieve symptoms	**Refer to doctor for intense, widespread itching** Antihistamines may provide some relief[16-18]

Key facts: Pruritis

Pruritis or itchiness is the consequence of loss of skin moisture.[19] In patients treated with sorafenib, it is usually associated with rash or xerosis.[2] It may be disruptive during sleep or waking hours.[4]

Stomatitis

Stomatitis (mouth inflammation) is a symptom of mucositis, a common side effect of sunitinib and sorafenib. The incidence varies, depending on the MKI, but this side effect may lead to dosage reductions that limit therapeutic benefit in a group of patients with advanced cancer.[4]

Prevention

Advise patients to:[20,21]

- Avoid cheek or lip biting
- Avoid mouth breathing
- Maintain god oral hygiene
- Maintain dentures by brushing daily and soaking in antimicrobial solution for at least 30 minutes/day and rinse thoroughly
- Avoid spicy and highly textured foods
- Avoid highly flavoured and alcohol-containing mouthwashes

Management

OTC therapy

For mild cases of mouth sores, pain, or redness on the inner cheeks, tongue, or lips

Meticulous oral hygiene:[20,21]

- Toothbrushing, 3-4 times daily with soft-bristle toothbrush. Soak toothbrush in warm water to soften bristles
- If brushing is painful, Toothettes (sponge-tipped stick with toothpaste), sponges, or gentle use of Waterpik®
- Biotene toothpaste is non-irritating contains natural salivary enzymes to control bacteria
- Floss gently once daily to avoid gum injury
- Salt and baking-soda rinses (1/2 teaspoon of each ingredient in 1 cup of warm water at least 4 times daily, especially after meals)
- Bland rinses, antimicrobial mouthwash
- OTC analgesics, such as ibuprofen (e.g., Advil®, Motrin®) and acetaminophen (e.g., Tylenol®)

Refer to doctor if patient has difficulty eating or drinking sufficient fluids or if redness is associated with lesions on the inner cheeks, tongue or lips[22]

Prescribed therapy

(moderate to severe cases):

- Topical fluoride (dentist)[20]
- Topical anesthetics[20]
- Corticosteroid solution[21]
- Topical or systemic analgesics[20]
- Topical or systemic antifungals[21]
- Palliative mixtures of various agents[20]

Key facts: Stomatitis

In patients treated with MKIs, the integrity of mucous membranes may be compromised, leading to the swelling and reddening of membranes lining the mouth. Mouth sores or cankers may develop. Patients may complain of changes on the inner cheeks or mouth surfaces, even when mouth sores are not present or only a mild redness is evident. Patients may experience:[4]

- Mouth pain
- Difficulty chewing
- Painful swallowing (dysphagia)

Maintaining mucosal health, integrity, and function is crucial in patients with stomatitis. Aggressive intervention can make a significant impact on this side effect.[4] Treatment aims to relieve symptoms until the mucous membranes can rejuvenate, usually within 7 to 14 days. Smokers have a greater risk of stomatitis.[21]

There are no evidence-based guidelines for the prevention or treatment of MKI-induced stomatitis, and experts tend to follow the clinical practice guidelines for chemotherapy- or EGFR-induced oral mucositis.[20-22]

Clinical practice guidelines stress the importance of oral hygiene in cancer patients, but due to a lack of supportive evidence, methods are usually based on personal preference and anecdotal experience.[20]

Good oral hygiene:[20,21]

- Reduces the severity of stomatitis
- Reduces mouth pain
- Reduces oral bleeding
- Reduces the risk of dental complications
- Minimizes the risk of soft tissue infections
- Enables patients to maintain a nutritious diet

The use of chlorhexidine mouth rinses is not recommended.

- They contain alcohol and may sting. Dilution defeats their antibacterial benefits.[20]

Hydrogen peroxide rinses may worsen mouth ulcers.[20]

Topical preparations in widespread use for chemotherapy-induced stomatitis contain ingredients such as lidocaine, benzocaine, milk of magnesia, kaolin, pectin, and diphenhydramine. There is no significant evidence of the effectiveness or tolerability of these concoctions, and some may be only minimally better than saline rinses. Clinical trials in chemotherapy patients with stomatitis have shown no difference in the effectiveness of chlorhexidine mouthwash, "magic" mouthwashes that contain lidocaine, and salt-and-baking soda rinses.[20]

Diarrhea

Diarrhea is common in sorafenib- and sunitinib-treated patients. Up to 55% of patients on sorafenib and about 53% of patients on sunitinib have diarrhea.[1,2] Dietary modifications are not recommended in anticipation of diarrhea.[23]

Prevention	No prevention measures are recommended.
Management OCT therapy[24] **Refer to doctor if moderate diarrhea does not improve after 24 hours of treatment**	Aggressive use of loperamide (e.g., Imodium®) for early-onset diarrhea **Mild to moderate (less than 4 loose stools per day)** • Follow instructions on package insert: 2 tablets immediately, then 1 tablet after each liquid bowel movement (maximum: 8 tablets/24 hours) **Moderate (more than 4 to 6 loose stools per day or night-time diarrhea)** • 2 tablets immediately, then 1 tablet every 2 hours during the day and 2 tablets every 4 hours during the night until bowel movements are normal for at least 12 hours • **This dosage is higher than packaging recommendations. Advise your patients that it is important to take the medication at higher doses to stop diarrhea**
Replace lost fluids[23-25]	• Fluid intake is more critical than food intake in patients with diarrhea. To replace lost fluid, advise patients with no contraindication to increase intake by up to 3 to 4 litres per day. • Drink several types of fluid, including plain water and electrolyte-containing drinks, such as clear broth, gelatin desserts, sports drinks, flat soft drinks, or decaffeinated tea
Anal care[23]	Advise patients to: • Clean the anal area with mild soap and warm water after each bowel movement to prevent irritation • Apply a barrier cream or ointment, such as petroleum jelly or Isle's paste • Soak in a warm bathtub or sitz bath to relieve discomfort • Examine the anal area for red, scaly or broken skin
Diet[4,24]	Advise patients to: • Advise patients to eat and drink small quantities of food often • Avoid spicy, greasy, or fried foods • Follow the BRAT (banana, rice, applesauce, toast) diet, along with clear liquids, until diarrhea begins to resolve • Avoid cabbage, Brussels spouts, and broccoli, which may produce stomach gas, bloating and cramps

Key facts: Diarrhea

There are no evidence-based guidelines for the prevention or treatment of diarrhea in patients taking MKIs. Antidiarrheal medications are usually able to control this dose-related side effect.[16]

- Loperamide is standard in mild to moderate cases at dosage intervals and levels recommended for uncomplicated EGFR- and chemotherapy-induced diarrhea.

When patients seek OTC treatment for diarrhea, it is important to ask them about:[23-25]

- Number of stools per day and stool composition, e.g., watery, presence of blood, nocturnal
- Presence of diarrhea before their last treatment
- Medication profile to identify other agents that may contribute to diarrhea
- Dietary profile
- Signs and symptoms of complicated diarrhea, including:
  - Blood in stool
  - Dehydration, e.g., oral dryness, low urine production or dark yellow urine, weight loss, dry eyes or mouth, sunken eyes, low pulse, dizziness or feeling faint when getting up
  - Fever
  - Lethargy or altered mental state
  - Nausea and vomiting
  - Signs of infection
  - Stomach cramps

References

1. Sorafenib product monograph. Bayer Inc. September 20, 2008.
2. Sunitinib product monograph. Pfizer Canada. August 13, 2008.
3. Krause DS, Va Etten RA. Tyrosine kinases as targets for cancer therapy. New Engl J Med 2005;353:172-187.
4. Wood LS. Managing the side effects of sorafenib and sunitinib. Comm Oncol 2006;3:558-562.
5. Rosenbaum SE, Wu S, Newman MA, West DP, et al. Dermatologic reactions to the multitargeted tyrosine kinase inhibitor sunitinib. Support Care Cancer 2008;16:557-566.
6. Hutson TE, Figlin RA, Kuhn JG, Motzer RJ. Targeted therapies for metastatic renal cell carcinoma: an overview of toxicity and dosing strategies. The Oncologist 2008;13:1084-1096.
7. Lacouture ME, Reilly LM, Gerami P, Guitart J. Hand foot skin reaction in cancer patients treated with the multikinase inhibitors sorafenib and sunitinib. Ann Oncol 2008;19:1955-1961.
8. Lacouture ME, Wu S, Robert C, Atkins MB, et al. Evolving strategies for the management of hand-foot skin reaction associated with the multitargeted kinase inhibitors sorafenib and sunitinib. The Oncologist 2008;13:1001-1011.
9. Rosenbaum SE, Wu S, Newman MA, West DP, et al. Dermatological reactions to the multitargeted tyrosine kinase inhibitor sunitinib. Support Cancer Care 2008;16:557-566.
10. Anderson R, Jatoi A, Robert C, Wood LS, et al. Search for evidence-based approaches for the prevention and palliation of hand-foot skin reaction (HFSR) caused by the multikinase inhibitors. The Oncologist 2009;14. Published online March 22, 2009.
11. Managing side effects of multi-kinase inhibitors. Caring for Oncology Patients: Tips and Tools for managing targeted therapy. Little Falls, NJ; Projects in Knowledge Inc., 2009.
12. Izzedine H, Ederhy S, Goldwasser F, Soria JC, et al. Management of hypertension in angiogenesis inhibitor-treated patients. Ann Oncol 2009;20:807-815.
13. Peréz-Soler R, Delord JP, Halper A, Kelly K, et al. HER1/EGFR inhibitor-associated rash: future directions for management and investigation outcomes from the HER1/EGFR inhibitor rash management forum. The Oncologist. 2005;10:345-356.
14. Lynch TJ, Kim ED, Eaby B, Garey J, et al. Epidermal growth factor receptor inhibitor-associated cutaneous toxicities: an evolving paradigm in clinical management. The Oncologist 2007;12:610-621.
15. Segaert S, Custem EV. Clinical signs, pathophysiology, and management of skin toxicity during therapy with epidermal growth factor inhibitors. Annals of Oncology 2005;16:1425-1433.
16. Quintás-Cardema A, Cortés JE, Kantarjian H. Practical management of toxicities with tyrosine kinase inhibitors in chronic myeloid leukemia. Clin Lymphoma Myeloma 2008;8(suppl3):S82-S88.
17. Guilhot F. Indications for imatinib mesylate therapy and clinical management. The Oncologist. 2004;9:271-281.
18. Deininger MWN, O'Brien SG, Ford JM, Druker BJ. Practical management of patients with chronic myeloid leukemia receiving imatinib. J Clin Oncol. 2003;21:1637-1647.
19. Lacouture ME, Boerner SA, LoRusso PM. Non-rash skin toxicities associated with novel targeted therapies. Clinical Lung Cancer 2006;8(1):S36-S42.

20. Rubenstein EB, Peterson DE, Schubert M, Keefe D, et al. Clinical practice guidelines for the prevention and treatment of cancer therapy-induced oral and gastrointestinal mucositis. Cancer. 2004;100(9) suppl:2026-2046.
21. Rosenbaum EH, Silverman S, Festa B, Rosenbaum I, et al. Mucositis: chemotherapy problems and solutions. Cancer Supportive Care Programs. October 2007. Accessed online at: www.cancersupportivecare.com/drug.php.
22. Morse L, Calarese P. EGFR-targeted therapy and related skin toxicity. Seminars in Oncology Nursing 2006;22(3):152-162.
23. Wadler S. Diagnosis and management of cancer-treatment-induced diarrhea. Clin Colorectal Cancer 2005;4:382-383.
24. Saltz LB. Understanding and managing chemotherapy-induced diarrhea. Supportive Oncology 2003;1:35-46.
25. Richardson G, Dobish R. Chemotherapy-induced diarrhea. J Oncol Pharm Pract 2007;13:181-198.

Overview of mTOR inhibitors

This chapter contains information on the prevention and management of common side effects of mTOR inhibitors that you are likely to encounter among cancer patients in your practice.

There are no evidence-based guidelines on how to manage mTOR-induced side effects. The recommendations presented here are based on a review of expert opinion and best practices in oncology. For a complete description of all side effects of these agents, please consult the product monographs.[1,2] Infusion reactions, which may occur with intravenous medications, are usually encountered in the clinic or hospital setting and will not be described here.

mTOR inhibitors

Everolimus (Afinitor®)
Temsirolimus (Torisel®)

Two medications are available that inhibit the action of the mammalian target of rapamycin (mTOR) signaling network. The route of delivery, dosing schedule, and side effects of these medications differ.[1,2]

Everolimus is an oral medication under investigation in a number of cancers. It is only available in Canada through the Expanded Access Program.[1,3] Temsirolimus is administered by intravenous infusion in the hospital or clinic setting.[2]

mTOR in cancer

In the 1970s, rapamycin, a natural product with antiproliferative effects, was discovered in the soil of an Easter Island. Two decades later, the mammalian target of rapamycin (mTOR) was identified as a serine-threonine protein kinase that regulates a cell-signaling pathway that controls cell-cycle progression, cell proliferation, and angiogenesis.[4,5]

The mTOR signaling pathway is incredibly complex, but one of its essential functions is to balance growth factor and nutrient signals. Growth factors activate mTOR, whereas low nutrient availability, e.g., low glucose or oxygen supplies, inhibits mTOR. When well regulated, this signaling network ensures that cell growth occurs under favourable conditions. When conditions are unfavourable, mTOR slows growth.[5]

The mTOR pathway acts like an on-off switch to regulate cell-cycle progression (cell division) in response to growth signals. It regulates the:[5]

- Cellular machinery that controls protein synthesis
- Proteins that control cell division
- Tumour suppressor functions that control new blood-vessel growth and cell survival

Drug administration

Everolimus

- This medication should be swallowed at the same time once daily with or without food. Advise your patients not to chew or crush the tablets.[1]

Temsirolimus

- This medication is administered as an intravenous infusion (once weekly) in the hospital or clinic setting.[2]

How to take mTor inhibitors

- Avoid grapefruit, grapefruit juice, star fruit, or Seville oranges while taking mTor inhibitors.[1,2]
- Avoid live vaccines and close contact with people who receive them. Examples of live vaccines include BCG, varicella, yellow fever, typhoid, mumps, measles, and rubella.[1,2]

Mechanism of action

Within the cell, everolimus and temsirolimus bind to a specific protein, FKBP-12, to produce a protein-drug complex. This complex binds to the mTOR kinase to neutralize its activity.[1,2,5,6]

Because the mTOR pathway is dysfunctional in many cancers, mTOR has become an important target for therapy.[5] In cancer cells, deactivation of the mTOR signaling network by mTOR inhibitors induces cell death and suppresses:[4,5]

- Protein synthesis (cell growth)
- Cell proliferation
- Angiogenesis
- Spread of cancer cells

Basic pharmacokinetics

Both mTOR inhibitors are metabolized by the CYP3A4 pathway, and co-administration with CYP3A4/5 inducers and inhibitors should be avoided.[1,2] Temsirolimus inhibits the metabolism of CYP3A4/5 substrates. Both medications are moderate inhibitors of the multidrug efflux pump PgP and mixed inhibitors of CYP2D6.[1,2]

Patients who miss a dose of everolimus may still take it up to 6 hours after their usual time. After more than 6 hours, they must skip the dose for the day. They should not take 2 doses on the next day to make up for the missed dose.[1]

Prevention and management of common side effects

The onset and duration of common side effects of mTor inhibitors are often predictable and almost always reversible after treatment ends. There are many ways to minimize or prevent these side effects.[1,2] The common side effects of everolimus generally appear to be similar in type and severity to those of temsirolimus.[1,2,6]

Because mTor plays a key role in glucose and lipid metabolism, patients may develop glucose intolerance/hyperglycemia and hyperlipidemia while taking mTor inhibitors. At least one study has correlated these side effects with successful mTor inhibition – an indication that this therapy is working. Since patients who take mTor inhibitors have advanced cancer, it is preferable to control the side effects than to reduce the therapeutic dosage or stop treatment.[5,6] The following table lists the common side effects of both mTor inhibitors.[1,2]

Common side effects of mTOR inhibitors

Click on side effects highlighted in blue for more information and click on the arrow to return.

General disorders
- Fatigue
- Headache
- Pain (arms & legs, chest, back, abdomen, joints)
- Sleeplessness
- Taste disturbance
- Weakness (asthenia)
- Weight loss

Gastrointestinal disorders
- Anorexia
- Diarrhea
- Mucositis
- Nausea and vomiting
- **Stomatitis**

Cardiovascular disorders
- Fluid retention (edema)

Respiratory disorders
- Cough, lung or breathing problems, shortness of breath

Blood disorders
- Low red blood cell count

Infection
- Fever
- Sore throat

Bleeding disorders
- Nose bleed

Skin disorders
- **Rash**, dry skin, pruritis

Metabolic disorders
- **Hyperglycemia**
- **Hyperlipidemia**

Serious side effects of mTor inhibitors are:[1,2,7]

- Gastrointestinal perforation
- Hematologic abnormalities, including anemia, myelosuppression, neutropenia, thrombocytopenia
- Infection
- Interstitial lung disease (shortness of breath, fever, cough)
- Metabolic abnormalities, including hyperlipidemia and hyperglycemia
- Renal failure (low urine output, body swelling, fatigue, abdominal pain)
- Stroke
- Wound-healing complications

Hyperglycemia

Hyperglycemia and glucose intolerance are common side effects of mTor inhibitors. Up to 50% of patients taking everolimus and up to 80% with temsirolimus (16% grade 3 and 4) have developed hyperglycemia in phase III trials.[1]

Monitoring	Advise patients, particularly those at risk for diabetes, to watch for the following symptoms and, if they appear, report them to their doctor:[2] • Frequent urination • Thirstiness • Feeling tired	
Management	Encourage patients to monitor blood glucose levels during treatment[7] Refer patients to a certified diabetes educator if available in the community or at the cancer center[7]	**Prescribed therapy** • Oral hyporglycemic agent and/or insulin[8]

Key facts: Hyperglycemia

Both oral and intravenous mTor inhibitors may raise blood glucose levels. Close monitoring of fasting blood glucose levels and hemoglobin A_{1c} and early intervention for hyperglycemia are recommended.[6].Patients with pre-existing diabetes may require dosage adjustments to oral hyperglycemic medications and/or insulin.[7]

Infection

From 25% to 37% of patients taking mTOR inhibitors may develop an infection.[1,2]

Prevention	Advise patients to:[1,2,7] • To wash their hands frequently and avoid crowded areas • Avoid live vaccines or close contact with people who receive live vaccines, e.g., intranasal influenza, measles, mumps, rubella, oral polio, bacillus Calmette-Guérin, yellow fever, TY21a typhoid	
Management	Advise patients to:[7] • Know whom to contact if their temperature rises above 38° Celsius for more than 1 hour or they have a one-time reading of 38.3° Celsius **Refer all patients with signs of infection for immediate care**	Prescribed therapy depends on type and severity of infection

Key facts: Infection

Because mTOR inhibitors suppress the immune system, patients may be especially vulnerable to opportunistic infections, such as herpes simplex, urinary tract infections, and upper respiratory infections.[7]

Non-infectious pneumonitis

Patients on mTOR inhibitors may develop a non-infectious pneumonitis. Symptoms may be similar to respiratory tract infection and include:[1,2]

- Shortness of breath
- New or worsening respiratory symptoms
- Cough
- Fever
- Feeling out of breath

Refer patients to a doctor immediately.

Stomatitis

In patients treated with mTOR inhibitors, the integrity of mucous membranes in the mouth and gastrointestinal tract may be compromised, leading to inflammation.[1,2,5] This side effect occurs in up to 44% of patients and can be a dose-limiting condition.[1,2,5]

Prevention

Advise patients to:[9]

- Avoid cheek or lip biting
- Avoid mouth breathing
- Maintain good oral hygiene
- Maintain dentures by brushing daily and soaking in antimicrobial solution for at least 30 minutes/day and rinse thoroughly
- Avoid spicy and highly textured foods
- Avoid highly flavoured and alcohol-containing mouthwashes

Management

OTC treatment

For mild cases of mouth sores, pain, or redness on the inner cheeks, tongue, or lips

Meticulous oral hygiene:[10-12]

- Toothbrushing, 3-4 times daily with soft-bristle toothbrush. Soak toothbrush in warm water to soften bristles
- If brushing is painful, Toothettes (sponge-tipped stick with toothpaste), sponges, or gentle use of Waterpik®
- Biotene toothpaste is non-irritating contains natural salivary enzymes to control bacteria
- Floss gently once daily to avoid gum injury
- Salt and baking-soda rinses (1/2 teaspoon of each ingredient in 1 cup of warm water at least 4 times daily, especially after meals)
- Bland rinses, antimicrobial mouthwash
- OTC analgesics, such as ibuprofen (e.g., Advil®, Motrin®) and acetaminophen (e.g., Tylenol®)

Refer to doctor if patient has difficulty eating or drinking sufficient fluids or if redness is associated with lesions on the inner cheeks, tongue or lips[13]

Prescribed medication

(moderate to severe cases):

- Topical fluoride (dentist)[10]
- Topical anesthetics with or without topical corticosteroids[11,13]
- Topical or systemic analgesics[10]
- Topical antifungals are preferable if a fungal infection is diagnosed[11]
- Palliative mixtures of various agents[10]

Key facts: Stomatitis

Changes in the oral cavity differ from those in patients treated with traditional chemotherapy. Mouth ulcers (cankers) often appear on the tongue, inside the lips, or inside cheeks. The ulcers do not appear to be contagious.

Maintaining the health, integrity, and function of oral mucosa is crucial in patients with stomatitis. Treatment aims to relieve symptoms, until the mucous membranes can rejuvenate themselves, usually within 7 to 14 days. Smokers have a greater risk of stomatitis.[11]

There are no evidence-based guidelines for treatment of mTOR inhibitor-induced stomatitis, and practitioners usually follow the common practices for chemotherapy-induced mouth inflammation. The guidelines stress the importance of good oral hygiene but, due to a lack of supportive evidence, oral hygiene methods are usually based on personal preference and anecdotal experience.[10]

Good oral hygiene:[10,11]

- Reduces the severity of stomatitis
- Reduces mouth pain
- Reduces oral bleeding
- Reduces the risk of dental complications
- Minimizes the risk of soft tissue infections
- Enables patients to maintain a nutritious diet

The use of chlorhexidine mouth rinses is not recommended.

- They contain alcohol and may sting. Dilution defeats their antibacterial benefits.[11]

Hydrogen peroxide rinses may worsen mouth ulcers.[11]

Topical preparations in widespread use for stomatitis contain ingredients such as lidocaine, benzocaine, milk of magnesia, kaolin, pectin, and diphenhydramine. There is no significant evidence of the effectiveness or tolerability of these concoctions, and some may be only minimally better than saline rinses. Clinical trials in chemotherapy patients with stomatitis have shown no difference in the effectiveness of chlorhexidine mouthwash, "magic" mouthwashes that contain lidocaine, and salt-and-baking soda rinses.[10]

Hyperlipidemia

mTOR inhibitors may increase cholesterol and triglyceride levels. In studies of everolimus, 77% of patients had higher levels of cholesterol and 73%, higher triglycerides.[1] In patients taking temsirolimus, up to 87% had higher levels of cholesterol and 83% had higher triglycerides.

Prevention	Counsel patients about dietary modification.[6]
Management	**Prescribed therapy** • Dietary modification • Appropriate lipid-lowering therapy

Key facts: Hyperlipidemia

Due to the possibility of drug interaction, patients who take mTOR inhibitors and statins have a greater risk of rhabdomyolysis – the breakdown of muscle cells that leads to kidney failure.[2]

Risk of rhabdomyolysis

Tell patients taking mTor inhibitors and statins to report any sign of muscle pain or weakness to their doctor, as this could be a sign of rhabdomyolysis.[2]

Diarrhea

Diarrhea occurs in 27% to 30% of patients who take mTOR inhibitors.[1,2] mTOR inhibitor-induced diarrhea often has early warning signs. Early recognition and intervention may lead to a more favorable outcome.[14] Loperamide is recommended to treat moderate diarrhea (≥4 stools per day) in patients treated with targeted therapies.[1,14,15] Dietary modifications are not recommended in anticipation of diarrhea.[15]

Prevention	No prevention measures are recommended.
Management OCT therapy[16] **Refer to doctor if moderate diarrhea does not improve after 24 hours of treatment**	Aggressive use of loperamide (e.g., Imodium®) for early-onset diarrhea **Mild to moderate (less than 4 loose stools per day)** • Follow instructions on package insert: 2 tablets immediately, then 1 tablet after each liquid bowel movement (maximum: 8 tablets/24 hours) **Moderate (more than 4 to 6 loose stools per day or night-time diarrhea)** • 2 tablets immediately, then 1 tablet every 2 hours during the day and 2 tablets every 4 hours during the night until bowel movements are normal for at least 12 hours • **This dosage is higher than packaging recommendations. Advise your patients that it is important to take the medication at higher doses to stop diarrhea**
Replace lost fluids[14-16]	• Fluid intake is more critical than food intake in patients with diarrhea. To replace lost fluid, advise patients with no contraindication to increase intake by up to 3 to 4 litres per day. • Drink several types of fluid, including plain water and electrolyte-containing drinks, such as clear broth, gelatin desserts, sports drinks, flat soft drinks, or decaffeinated tea
Anal care[15]	Advise patients to: • Clean the anal area with mild soap and warm water after each bowel movement to prevent irritation • Apply a barrier cream or ointment, such as petroleum jelly or Isle's paste • Soak in a warm bathtub or sitz bath to relieve discomfort • Examine the anal area for red, scaly or broken skin
Diet[14]	Advise patients to: • Advise patients to eat and drink small quantities of food often • Avoid spicy, greasy, or fried foods • Follow the BRAT (banana, rice, applesauce, toast) diet, along with clear liquids, until diarrhea begins to resolve • Avoid cabbage, Brussels spouts, and broccoli, which may produce stomach gas, bloating and cramps

Key facts: Diarrhea

When patients seek OTC treatment for diarrhea, it is important to ask them about:[14,15]

- Number of stools per day and stool composition, e.g., watery, presence of blood, nocturnal
- Presence of diarrhea before their last treatment
- Medication profile to identify other agents that may contribute to diarrhea
- Dietary profile
- Signs and symptoms of complicated diarrhea, including:
  - Blood in stool
  - Dehydration, e.g., oral dryness, low urine production or dark yellow urine, weight loss, dry eyes or mouth, sunken eyes, low pulse, dizziness or feeling faint when getting up
  - Fever
  - Lethargy or altered mental state
  - Nausea and vomiting
  - Signs of infection
  - Stomach cramps

Rash

Rash is a very common side effect of mTOR inhibitors, occurring in 30% of patients on everolimus and 47% of those on temsirolimus. Most cases are mild to moderate in severity.[1,2,5,6]

Prevention

A proactive approach is critical in managing rash.[17] When patients begin therapy, advise them to:[17-19]

- Cleanse with mild soaps or cleaners or bath or shower oils to avoid skin dryness.
- Moisturize twice a day with thick, emollient-based creams, such as Aveeno® lotion, Neutrogena® Norwegian Formula hand cream, or Vaseline Intensive Care® Advanced Healing Lotion.
- Use only fragrance- , alcohol-, and dye-free lotions and cosmetics.
- Use a dermatologist-approved cover-up, such as Dermablend® or Cover FX®, to conceal the rash.
- Remove make-up with a gentle, skin-friendly cleanser, e.g., Neutrogena®, Dove®
- Use a broad-spectrum sunscreen (SPF 15 or greater) that contains zinc oxide or titanium dioxide.

Management	**Mild**[17] • Localized • Few symptoms • No impact on daily activities • No sign of infection	No treatment or: • Topical corticosteroids (e.g., hydrocortisone 0.5% cream)[17] • Mild soap and cleansers[20] • Moisturizers twice daily[20] **Advise patient to monitor the rash for changes in severity.**[1-4] **Refer to doctor if rash persists after 2 weeks of treatment or worsens in severity.**[17]	**Prescribed medications** • Topical agents with anti-inflammatory properties, such as hydrocortisone 1% to 2.5% cream, metronidazole cream or clindamycin 1% gel,[17]
	Moderate[17] • Generalized • Mild symptoms (e.g., pruritis, tenderness) • Minimal impact on daily activities **Refer to doctor.**	**Advise patient to monitor the rash for changes in severity.**[1,2] **Advise patient to consult doctor if symptoms persist or worsen after 2 weeks of treatment .**[17]	**Prescribed medications**[17,20] • Hydrocortisone 2.5% cream, clindamycin 1% gel, or pimecrolimus 1% cream PLUS • doxycycline (100-mg BID) or minocycline (100-mg BID)

Key facts: Rash

Skin rashes are usually spots or small raised bumps with or without fluid that appear on the chest, upper back and sometimes, the face.[6] The rash is not as severe as EGFR-related rash but tends to be treated by similar means.[6] Some experts also recommend the use of oral antihistamines.

References

1. Everolimus product monograph (USA). Novartis Pharmaceuticals Corp. March 2009.
2. Temsirolimus product monograph. Wyeth Canada. October 16,2008.
3. RAD001/Everolimus/Afinitor Expanded Access Trial. Kidney Cancer Research Network of Canada. April 15, 2009. Accessed at: www.kidneycancercanada.org/main.php?p=221.
4. The mTOR pathway as a new target. The Oncology Report. National Comprehensive Cancer Network. Accessed at: www.nccn.org/professionals/meetings/13thannual/highlights/1316.html.
5. Figlin RA, Brown E, Armstrong AJ, Akerley W, et al. NCCN Task Force Report: mTOR inhibition in solid tumours. JNCCN 2008;6(suppl 5):S1-S23.
6. Hutson TE, Figlin RA, Kuhn JG, Motzer RJ. Targeted therapies for metastatic renal cell carcinoma: an overview of toxicity and dosing strategies. The Oncologist 2008;13:1084-1096.
7. Managing side effects of mTOR inhibitors. Caring for Oncology Patients: Tips and Tools for managing targeted therapy. Little Falls, NJ; Projects in Knowledge Inc., 2009.
8. Bellmut J, Szczylik C, Feingold J, Strahs A, Berkenblit A. Temsirolimus safety profile and management of toxic effects in patients with advanced renal cell carcinoma and poor prognostic features. Ann Oncol 2008;19:1387-1392.
9. Regroupement des pharmaciens en oncologie. General information for patients. Protocol: Erlotinib. Conseil de lutte contre le cancer. APES. GEOQ. September 2005.
10. Rubenstein EB, Peterson DE, Schubert M, Keefe D, et al. Clinical practice guidelines for the prevention and treatment of cancer therapy-induced oral and gastrointestinal mucositis. Cancer. 2004;100(9) suppl:2026-2046.
11. Rosenbaum EH, Silverman S, Festa B, Rosenbaum I, et al. Mucositis: chemotherapy problems and solutions. Cancer Supportive Care Programs. October 2007. Accessed online at: www.cancersupportivecare.com/drug.php.
12. Cancer.Net. Dry mouth or xerostomia. February 2009. Accessed at: www.asco.org/patient/Diagnosis+Treatment/Treating+Cancer/Managing+Side+Effects/ci.Dry+Mouth+or+Xerostomia
13. Morse L, Calarese P. EGFR-targeted therapy and related skin toxicity. Seminars in Oncology Nursing 2006;22(3):152-162.
14. Saltz LB. Understanding and managing chemotherapy-induced diarrhea. Supportive Oncology 2003;1:35-46.
15. Richardson G, Dobish R. Chemotherapy-induced diarrhea. J Oncol Pharm Pract 2007;13:181-198.
16. Regroupement des pharmaciens en oncologie. General information for patients. Protocol: Erlotinib. Conseil de lutte contre le cancer. APES. GEOQ. September 2005.
17. Lynch TJ, Kim ED, Eaby B, Garey J, et al. Epidermal growth factor receptor inhibitor-associated cutaneous toxicities: an evolving paradigm in clinical management. The Oncologist 2007;12:610-621.

18. Peréz-Soler R, Delord JP, Halper A, Kelly K, et al. HER1/EGFR inhibitor-associated rash: future directions for management and investigation outcomes from the HER1/EGFR inhibitor rash management forum. The Oncologist. 2005;10:345-356.
19. Segaert S, Custem EV. Clinical signs, pathophysiology, and management of skin toxicity during therapy with epidermal growth factor inhibitors. Annals of Oncology 2005;16:1425-1433.
20. Widakowich C, De Castro G, De Azambuja E, Dinh P, Awada A. Review: Side effects of approved targeted therapies in solid cancers. The Oncologist 2007;12:1443-1455.

Overview of Vascular endothelial growth factor inhibitors

This chapter contains information on the prevention and management of common side effects of vascular endothelial growth factor (VEGF) inhibitors that you are likely to encounter among cancer patients in your practice.

One medication is available that inhibits the action of vascular endothelial growth factor (VEGF). Bevacizumab is combined with traditional forms of chemotherapy to treat several cancers in the advanced stage.[1]

Some medications that inhibit multiple kinases, particularly sunitinib and sorafenib, can also inhibit VEGF activity. These medications, which appear in the chapter on multiple kinase inhibitors (MKIs), may have similar side effects to bevacizumab. However, these MKIs are not exclusively used to inhibit VEGF.

VEGF inhibitor

Bevacizumab (Avastin®)

There are no evidence-based guidelines on how to manage VEGF inhibitor-induced side effects. The recommendations presented here are based on a review of expert opinion and best practices in oncology. For a complete description of all side effects, please consult the product monograph.[1]

VEGF in cancer

The formation of new blood vessels in an established circulatory system, a process known as angiogenesis, is a critical step in cancer development.[2,3] As tumours grow, the need for oxygen and nutrients outpaces the supply from nearby blood vessels. In response, they release VEGF, which increases the permeability of blood vessels near tumours, enabling plasma proteins and other large molecules to leak out of small blood vessels. These molecules form a fibrin gel, which acts as a supportive matrix for the endothelial cells and fibroblasts that form new blood vessels. The circulatory network that feeds tumours expands, enabling cancer to grow and progress.[3] VEGF is one of the body's most potent promoters of angiogenesis.[4] VEGF regulates tumour:[2,3]

- Angiogenesis
- Growth
- Progression

Drug administration

Bevacizumab is an intravenous infusion that is administered in the hospital or clinic setting.[1]

Mechanism of action

Bevacizumab is a monoclonal antibody that binds specifically to VEGF to neutralize its biological activity.[1] By binding to VEGF, bevacizumab prevents this protein from attaching to VEGF receptors on blood-vessel walls, thus preventing the changes in vascular permeability that are necessary for angiogenesis. In short, bevacizumab chokes off the blood supply to tumours.[5]

By neutralizing VEGF, bevacizumab:[1-3]

- Inhibits tumour angiogenesis
- Slows tumour growth
- Slows the spread of cancer

Basic pharmacokinetics

There are no formal drug interaction studies for bevacizumab.[1] Bevacizumab is not metabolized by the kidney or liver but is managed in the body like the natural antibody IgG.[1]

Exercise caution when combining bevacizumab with anticoagulant medication due to increased risk of bleeding.[1]

Prevention and management of common side effects

The common side effects of bevacizumab are predictable, generally mild to moderate, and manageable.[2] The following table summarizes the most common side effects (incidence ≥ 10%) of this VEGF inhibitor.[1,5]

Common side effects of VEGF inhibitors

Click on side effects highlighted in blue for more information and click on the arrow to return.

Blood and lymphatic disorders
- Neutropenia
- Febrile neutropenia
- Leucopenia
- Thrombocytopenia
- Infection

Cardiovascular disorders
- **Hypertension**

Eye disorders
- Increased tear production

Gastrointestinal disorders
- Diarrhea
- Nausea
- Vomiting
- Abdominal pain
- Constipation
- Stomatitis
- Rectal bleeding

General disorders
- Fatigue/loss of strength
- Joint pain
- **Minor bleeding (nose bleed)**
- Mucositis
- Pain
- Fever

Metabolic disorders
- Dehydration
- Anorexia

Nervous system disorders
- Headache
- Peripheral sensory neuropathy
- Taste disorder

Renal disorders
- Proteinuria

Respiratory disorders
- Dyspnea
- Nosebleeds
- Runny nose

Skin disorders
- Dry skin
- Exfoliative dermatitis
- Skin discolouration

Refer for medical attention

Some specific but uncommon side effects of bevacizumab may be severe and even life-threatening.[1,2]

Gastrointestinal perforation

- Patients with abdominal pain and constipation or vomiting need to seek immediate medical attention. Early detection of this life-threatening condition is essential.[2] This side effect generally occurs within the 60 days of treatment.[5]

Thrombosis

- Tell patients, particularly those >65 years or with a history of thrombosis, heart disease, or stroke, about the warning signs of blood clots in the lungs and arteries.[6]

Wound-healing complications

- Any patient with newly gaping or bleeding wounds or who have delayed wound healing should seek immediate medical attention.[2,6]

Hypertension

The onset of high blood pressure (hypertension) may occur at any time during bevacizumab therapy.[2] Most hypertension is manageable; less than 1% of patients have discontinued bevacizumab due to this side effect.[2]

Monitoring	Encourage patients to:[2,5-8] • Monitor their blood pressure (BP) at 2- to 3-week intervals or at more frequent intervals often if they already have hypertension	
Management	Refer for antihypertensive therapy[6] • Patients with recurrent, symptomatic, or persistent >20 mm Hg increase in diastolic BP	**Prescribed therapy** • Most hypertension can be managed with standard oral antihypertensive therapy.[2,6]

Key facts: Hypertension

Hypertension is the most common side effect of bevacizumab.[2]

- Up to 32% of cancer patients have experienced new or worsened hypertension.[2]
- Up to 16% patients have developed moderate to severe hypertension that required oral antihypertensive therapy or a change in dosage of existing antihypertensive medication.[2]

Patients on bevacizumab therapy are 8 to 9 times more likely to develop hypertension than others. Hypertension is often transient and typically resolves after therapy ends. It is more likely to occur and have more impact in patients who already have hypertension.

In patients with severe hypertension, persistent hypertension despite treatment, or who experience a hypertensive crisis, bevacizumab will be discontinued.[1,8] All patients on bevacizumab who develop hypertension should be screened for proteinuria.[8]

Bleeding

Minor bleeding from the skin and mucous membranes have occurred in 20% to 40% of patients on bevacizumab.[1]

Monitoring	Encourage patients to: • Monitor and report bleeding events to their doctor[6]
Management	Nosebleeds • Apply first-aid techniques for minor episodes • Refer to hospital for emergency care of bleeding events that require intervention

Key facts: Bleeding

Bleeding events are usually minor, occurring mostly as nosebleeds that respond to first-aid treatment and stop within 5 minutes.[2,6] Bleeding from the gums may occur, and women may have longer and heavier uterine bleeding during their periods. Tumour-related bleeding may also occur.[2,6] In certain cancers, life-threatening bleeding complications may occur in up to 9.4% of patients.[2,6]

Life-threatening hemorrhages have occurred in some patients. They are 5 times more likely to occur in patients treated with bevacizumab than others. Any bleeding event should be reported to the patient's doctor.[1,5]

For nosebleeds, the most common first-aid method is to instruct the patient to lean forward, pinching the bridge of the nose between thumb and forefinger until bleeding stops. If a nosebleed lasts longer than 10 to 15 minutes or the patient feels faint or dizzy, advise him or her to seek immediate care.[5]

References

1. Avastin® product monograph. Hoffman-La Roche Ltd. March 27, 2009.
2. Gordon MS, Cunningham D. Managing patients treated with bevacizumab combination therapy. Oncology 2005;69(suppl 3):25-33
3. Ribatti D. The crucial role of vascular permability factor/vascular endothelial growth factor in angiogenesis: a historical review. Br J Haematol 2004;128:303-309.
4. Gurevich F, Perazella MA. Renal effects of anti-angiogenesis therapy: update for the internist. Am J Med 2009;122:322-328.
5. Managing side effects of anti-VEGF treatment. Caring for Oncology Patients: Tips and Tools for managing targeted therapy. Little Falls, NJ; Projects in Knowledge Inc., 2009.
6. BC Cancer Agency Cancer Management Guidelines. Management guidelines of bevacizumab-related side effects. December 1, 2006. Accessed at: www.bccancer.bc.ca.
7. Adams VR. Guide for the administration and use of targeted cancer agents 2007/2008. McMahon Publishing; New York, 2008.
8. Izzedine H, Ederhy S, Goldwasser F, Soria JC, et al. Management of hypertension in angiogenesis inhibitor-treated patients. Ann Oncol 2009;20:807-815.

Quiz

Instructions

Final quiz and evaluation

In order to be eligible for continuing education credits, you must complete the **final quiz** with a minimum grade of 70% and complete the **program evaluation**.

Please note that you are permitted only **two attempts** at the final quiz. This final quiz is comprised of 27 multiple-choice questions and requires approximately 30 minutes complete.

Instructions pertaining to quiz and evaluation

Once you have completed the entire program, print the quiz and the evaluation. Complete the quiz questions and the evaluation questions.

Fax your completed quiz and evaluation to fax number: **306-545-7795**. Once you have successfully completed the program, you will receive your certificate of participation by email.

Note: The certificates will be emailed to you by CCCEP. They are sometimes filtered as "junk mail". Please check your "junk mail". If you have not received your certificate by email within 5 working days upon completing the quiz and program evaluation, please contact us: ***info@cccep.ca***.
For any difficulties, call: 306-545-7790

1. Alemtuzumab suppresses T cells, which may reactivate dormant viruses, including cytomegalovirus.
   a. True
   b. False

2. Rituxumab is rarely associated with opportunistic infections but is known to reactivate the following infection on rare occasions:
   a. Shingles
   b. Epstein-Barr virus
   c. Hepatitis B
   d. Cytomegalovirus

3. Patients cannot eat for at least 2 hours before and at least 1 hour after taking which medication?
   a. Dasatinib
   b. Imatinib
   c. Nilotinib

4. What is the most common side effect of Bcr-Abl inhibitors?
   a. Diarrhea
   b. Myelosuppression
   c. Rash
   d. Fluid retention

5. Which of the following medications must be used with caution in patients who take imatinib?

   a. Omeprazole
   b. Phenylephrine
   c. Low molecular weight heparin
   d. Acetaminophen

6. For moderate diarrhea, patients should use the following dosing regimen for loperamide during daytime hours until bowel movements are normal:

   a. 2 tablets immediately, then 1 tablet every 2 hours
   b. 2 tablets every 4 hours
   c. 2 tablets immediately, then 1 tablet every 4 hours
   d. 2 tablets immediately, then 2 tablets every 2 hours

7. Patients with diarrhea and no contraindications are advised to drink which quantity of fluids?

   a. 1 litre per day
   b. 2 to 3 litres per day
   c. 3 to 4 litres per day
   d. 5 litres per day

8. In patients taking Bcr-Abl inhibitors, which supplements may provide relief from muscle aches or cramps?

   a. St. John's wort
   b. Glucosamine
   c. Vitamin C
   d. Magnesium

9. Which of the following conditions rarely occurs in patients taking nilotinib or imatinib but happens in 14% to 30% of patients who take dasatinib.

   a. Pleural effusion
   b. Peripheral fluid retention
   c. Infection
   d. Rash

10. Both imatinib and sunitinib are primarily metabolized by which metabolic pathway?

    a. CYP2D6
    b. CYP3A4
    c. UGT1A9
    d. CYP2C9

11. Rash is more likely to occur in which subgroup of imatinib-treated patients?

    a. Women
    b. Adults > 45 years
    c. Adults on concurrent medication
    d. Men

12. Which of the following mouth rinses are recommended for the treatment of stomatitis?

    a. Chlorhexidine
    b. Hydrogen peroxide
    c. Salt and baking soda
    d. Lidocaine

13. Which of the following symptoms is a sign of complicated diarrhea?

    a. 4 stools per day
    b. Night-time diarrhea
    c. Fever
    d. Watery stool

14. _____ reduces exposure to erlotinib. (Fill in the blank)

    a. Cigarette smoking
    b. Acetaminophen
    c. Calcium channel blockers
    d. Grapefruit juice

15. After therapy begins, EGFR inhibitor-induced rash usually occurs:

    a. Within 1 to 3 weeks
    b. Within 1 month
    c. Within 4 to 6 weeks
    d. Within 3 months

16. Which of the following medications are recommended for mild EGFR inhibitor-induced rash?

    a. Benzoyl peroxide
    b. Retinoids
    c. Alpha-hydroxyacids
    d. Topical hydrocortisone 0.5% cream

17. Which of the following medications can be used to treat hamburger-like bumps in patients with paronychia?

    a. Epsom salts
    b. Topical antibiotics
    c. Topical silver nitrate
    d. Topical hydrocortisone 0.5% cream

18. In patients taking multi-kinase inhibitors, patients should be monitored for high blood pressure:

    a. Daily for the first 3 weeks
    b. Weekly for the first 6 weeks
    c. Once every 2 weeks
    d. Monthly

19. The bioavailability of which medication is 29% lower when eaten with a high-fat meal?

    a. Sorafenib
    b. Imatinib
    c. Sunitinib
    d. Erlotinib

20. Which constellation of symptoms is characteristic of hand-foot skin reaction in patients on multi-kinase inhibitors?

    a. Symmetrical changes in skin sensation
    b. Swelling
    c. Generalized redness
    d. Localized callus-like skin

21. The HER2 receptor is overexpressed on cell surfaces or continuously activated in what percentage of breast cancers?

    a. 25-30%
    b. 35-40%
    c. 50-60%
    d. 65-70%

22. Which of the following medications must be taken on an empty stomach?

    a. Everolimus
    b. Cetuximab
    c. Lapatinib
    d. Gefitinib

23. Patients who take mTOR inhibitors are advised to avoid:

    a. Milk
    b. Live vaccines
    c. Acetaminophen
    d. Smoking

24. Patients who take mTOR inhibitors have a 50% to 80% risk of developing which of the following conditions?

    a. Rash
    b. Infection
    c. Hyperglycemia
    d. Stomatitis

25. Shortness of breath, cough, and fever may signal which life-threatening condition in patients taking mTOR inhibitors?

    a. Cardiac arrest
    b. Non-infectious pneumonitis
    c. Myelosuppression
    d. Thrombocytopenia

26. Bevacizumab is a monoclonal antibody that binds to VEGF to:

    a. Inhibit tumour angiogenesis
    b. Induce apoptosis
    c. Disrupt transcription of oncogenes
    d. Activate the immune system

27. How often should patients on bevacizumab who have no history of hypertension monitor their blood pressure?

    a. Weekly
    b. Every 2 to 3 weeks
    c. Every 3 to 4 weeks
    d. Every 6 weeks

Thank you for your participation

Fax your completed quiz to: **306-545-7795.**

Program Evaluation

Please print and complete the following program evaluation. Once complete, fax evaluation along with your completed Final Quiz in order to obtain your CEU credits and a certificate of attendance. Note that this is an anonymous evaluation and as such, your personal information will not be related to your comments.

1. How would you rate this program on an overall basis?

   Poor **Fair** **Good** **Very Good** **Excellent**

2. What were the most valuable ideas you learned in this program? To what degree will your practice change as a result of your participation in this online educational program?

   _____

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   _____

3. Answer the item statements about this program according to the ratings provided (1=poor, 2=fair, 3=good, 4=very good, 5= excellent)

Item Statements	Poor	Fair	Good	Very Good	Excellent
Program met the stated learning objectives	1	2	3	4	5
Program met my expectations	1	2	3	4	5
Content of the program	1	2	3	4	5
Quality of visuals	1	2	3	4	5
Program was credible and non-biased	1	2	3	4	5
Ease of using PDF-based format for learning	1	2	3	4	5

4. Please make any additional comments that would help us to plan future online learning programs and that may improve the learning experience.

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