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Title: Cardiac Toxicity of Sunitinib and Sorafenib in Patients With Metastatic Renal Cell Carcinoma.

Background:

- Sunitinib and sorafenib are tyrosine kinase inhibitors (TKI) with efficacy in a variety of tumours. Sunitinib is the reference standard first line treatment for clear cell renal cell carcinoma while sorafenib improves PFS when used in the second line.
- The frequency and reversibility of cardiotoxicity associated with the use of sorafenib and sunitinib has not been well studied. Published phase III trials have not included cardiac endpoints and the identification of cardiac adverse effects has been predominantly based on the occurrence of clinical symptoms.
- This current article investigates rates of sunitinib or sorafenib cardiotoxicity, its reversibility and the ability of patients experiencing cardiotoxicity to continue TKI therapy.

Study design:

- Observational, single-centre study (Austria)
    - 86 patients received sunitinib or sorafenib for metastatic renal cell carcinoma between March 2006-June 2007:
        - 74 were evaluable for cardiotoxicity

    - Baseline variables assessed:
        - Coronary artery risk factors
        - History or evidence of coronary artery disease (CAD)
        - Hypertension
        - Rhythm disturbances
        - Heart failure

    - Cardiac Monitoring:
        - History for symptom assessment:
            - Baseline, then twice a month
            - Asked about dyspnea on exertion, typical angina and dizziness
        - Blood pressure:
            - Baseline in clinic
            - Self monitoring tid
        - ECGs:
            - Baseline, then monthly
            - Also done if symptomatic or with elevated cardiac enzymes
        - Cardiac enzymes:
            - Tpn-T, CK, CK-MB

        - Baseline, then twice a month or if symptomatic
    - Echocardiography:
        - Baseline if had a history of chest pain, dyspnea on exertion, edema, pleural effusions, MI, CHF, or arrhythmia
        - Also did in all subjects having cardiac events defined as:
            - New left ventricular dysfunction (LVEF ≤56%)
            - Increased cardiac enzymes if normal at baseline
            - Symptomatic arrhythmia
            - Acute coronary syndrome

- Endpoints:
    - Cardiac event rate (asymptomatic vs symptomatic)
    - Degree of reversibility of cardiac event
    - Ability to continue TKI therapy if had cardiac event

Study results:

- Patient Characteristics:
    - Median age 66 (range 46-86)
    - Received sunitinib, sorafenib or both sequentially during study
    - Previous treatments:
        - Cytokines 75.6%
        - Targeted therapies: bevacizumab 7%
    - 67% ECOG 0

Cardiac History at baseline		Cardiac Risk Factors at baseline	
CAD	9.3%	HTN	49%
MI	5.8%	NIDDM	22%
CHF	7%	↑ Cholesterol	26.7%
Rhythm Disturbance	3.5%	↑ Triglycerides	12.8%
Uncontrolled HTN	3.5%	Current/ex smoker	16.3%

- Cardiac Outcomes:

	n (%)
Cardiac Events	25 (33.8)
Left ventricular dysfunction at event (LVEF ≤56%)	12 (16.2)
Increased Tpn-T ± CK-MB with event	22 (29.7)
Clinical cardiac symptoms with event	13 (17.6)
Cardiac compromise needing CCU/ICU	7 (9.4)
ECG changes	30 (40.5)

- Sunitinib and sorafenib subjects had 11 and 14 cardiac events respectively
- Median duration of TKI treatment at event was 8 weeks (range 2-48 weeks)

- All patients undergoing a cardiac event recovered with cardiac interventions, including medical treatment, pacemaker, coronary angiography or heart surgery
- All patients were considered eligible for TKI continuation in conjunction with cardiac medications
- There was no difference in survival depending on whether or not patients had a cardiac event
- Hypercholesterolemia and hypertriglyceridemia were the only variables significantly more pronounced among patients who had a cardiac event compared to those who did not (but small numbers may not have had enough power to detect associations. . .)

Conclusions:

- Rates of cardiac events in patients receiving TKIs are higher than previously appreciated. 33.8% of all patients had a cardiac event (16.2% asymptomatic and 17.6% symptomatic)
- With appropriate cardiac treatment, all patients recovered and could continue treatment
- Prior cardiac history was not predictive of cardiac events
- Cardiac events did not appear to have a negative impact on survival

Study commentary:

- The paper does not actually say how many patients were on sunitinib versus sorafenib therefore it is difficult to draw conclusions as to whether one TKI appears more cardiotoxic than the other
- Important to be aware of risk for cardiac sequelae with TKI use, especially as many of the symptoms may be falsely attributed to oncologic disease progression and interpreted as disease progression
- TKIs are also associated with hypertension, which can increase the risk for cardiac events
- This paper failed to report the rate of congestive heart failure, which should be included as a clinically relevant endpoint
- The fact that all patients recovered and were felt to be eligible to continue treatment is interesting
- Need to define the extent and nature of screening with cardiac enzymes, ECGs, etc detect cardiac toxicity and provide treatment in a timely manner
- As we continue to better understand the mechanisms by which TKIs contribute to cardiac toxicity/dysfunction, we should be able to better target our cardiac therapies. Some investigators have suggested cardiac mitochondrial dysfunction, and if this is the case, medications targeting the mitochondria may be beneficial. These include beta-blockers (e.g. carvedilol) and statins (e.g. simvastatin)

Website link to source: *www.jco.org epub ahead of print Oct 6, 2008*