ONCOLOGYEDUCATION.CA
Improving patient care through education.

LATEST ONCOLOGY UPDATES

Title: Impact of Androgen Deprivation Therapy on Cardiovascular Disease and Diabetes

Background:

- Approximately half of men with prostate cancer receive androgen deprivation therapy (ADT). Most remain on treatment for a minimum of 2-3 years
- ADT has significant associated adverse effects, including worse quality of life, sexual dysfunction, fatigue, anemia, loss of bone density and fractures
- Data on the potentially increased risk for cardiovascular disease (acute MI or cardiac death) and diabetes among men receiving ADT has been conflicting

Study design:

- Matched cohort study using linked administrative data:
  - Ontario Cancer Registry (OCR) used to identify cases
  - Used provincial health card number to link to subject data in other databases at the Institute for Clinical Evaluative Services (ICES) in Ontario
- Study Cohort:
  - Men diagnosed with prostate cancer between Jan 1, 1995 and Dec 31, 2005
  - Age 66 or older (drug claim database collection starts at age 65, thus ensuring one year of drug data available)
  - Patients who received ADT were paired with subjects with prostate cancer who did not receive ADT based on "propensity score matching"
  - The propensity score matching model was used to balance the distribution of possible confounders between patients receiving ADT vs those who did not, factoring in:
    - Age, year of diagnosis
    - Comorbidities, medication use
    - Socioeconomic factors
  - ADT users were defined as those who received at least 6 months of continuous medical ADT (either LHRH agonists, nonsteroidal antiandrogens, or steroidal antiandrogens) or those who underwent orchiectomy
- Endpoints:
  - Primary:
    - Development of myocardial infarction (MI)
    - Sudden cardiac death (SCD)
    - Development of diabetes mellitus (DM)
  - Secondary:
    - Incident fractures (excluding patients with bone metastases)
    - Development of a vascular event:
      - stroke, congestive heart failure (CHF), use of diagnostic coronary angiography or cardiovascular revascularization

Study results:

- Patient Characteristics:
  - 116,769 patients had prostate cancer in the OCR

        - 24,518 of these patients were eligible ADT users
    - A non-ADT user match was identified for 19,079 patients
        - thus the total number of subjects was n=38,158
    - Subjects were well balanced with respect to baseline characteristics
    - The mean age was 75.0 years (SD 6.3)
- Primary Outcomes:
    - The median duration of follow up was 6.47 years

	ADT users	Non ADT users	HR (95% CI)	P value
Myocardial Infarction	949 (4.7%)	1085 (5.5%)	HR 0.92 (0.84-1.00)	0.059
Sudden Cardiac Death	399 (2.0%)	436 (2.2%)	HR 0.96 (0.83-1.10)	p=0.53
Diabetes	1,392 (7.1%)	1,181 (6.0%)	**HR 1.26** (1.16-1.36)	**p<0.0001**

    - More patients developed Diabetes in the ADT group
    - On multivariate analysis, the following features were found to be predictive of myocardial infarction or sudden cardiac death
        - Use of aspirin or a prior diagnosis of DM, hypertension, dyslipidemia, chronic kidney disease, MI or coronary artery disease
    - In addition to ADT use, prior diagnosis of hypertension was also associated with a higher incidence of new diabetes
- Secondary Outcomes:

	ADT users	Non ADT users	HR (95% CI)	P value
Fractures • Fragility • Any fractures	 1,778 (9.0%) 3,387 (17.2%)	 1,157 (5.9%) 2,495 (12.7%)	 **HR 1.65** (1.53-1.78) **HR 1.46** (1.39-1.54)	 **p<0.0001** **p<0.0001**
Vascular Outcomes • CHF • Stroke • Diag Cardiac Cath • Revascularizat n	 12.7% 5.4% 6.0% 3.6%	 13.8% 6.4% 7.2% 4.4%	 0.95 0.88 0.88 0.87	 0.057 **0.001** **0.001** **0.005**

    - More patients developed fractures in the ADT group
    - More patients had a stroke or required diagnostic cardiac catheterization or revascularization in the non ADT group

Conclusions:

- In this large review of administrative databases in Ontario it was found that ADT use in men with prostate cancer was associated with an increased risk of incident diabetes, but not with an excess risk of MI or SCD
- Secondary outcomes showed an increased risk of fragility fractures, but no increased risk of CHF among ADT users
- Secondary outcomes showed a lower likelihood of stroke and of undergoing invasive diagnostic or therapeutic cardiac procedures among ADT users

Study commentary:

- Study Strengths:
    - Canadian study
    - Very large cohort with larger absolute number of events compared to previous studies
    - Median age of 75 representative of a typical prostate cancer cohort
    - Use of large database based on standardized ICD definitions
- Study Limitations:
    - Limitations inherent to study design:
        - Assume patients took medications as prescribed
        - Assume all relevant events were captured
    - Didn't look at younger men
    - Didn't capture/control for chemotherapy use:
        - E.g. Mitoxantrone associated with cardiotoxicity
        - E.g. Steroids used with docetaxel may aggravate glucose intolerance
    - Didn't capture/control for smoking
    - Didn't describe reason for initiating ADT or stage of patients being treated – implied only in "Results" that excluded patients with metastasis: "149 men were excluded because of a diagnosis of bone metastases before ADT use . . .". This makes it difficult to know how generalizable the results are
- Interpretation of Results:
    - Didn't just fail to find increased risk for cardiovascular events, but unexpectedly, ADT appeared protective (strokes, diagnostic catheterizations and revascularization)
    - How to account for cardiovascular "protective" effect:
        - Patients receiving ADT more likely to have regular contact with primary care physician for administration of ADT (e.g. LHRH agonist injections), and thereby more likely to have their cardiac risk factors managed
        - Other variables not accounted for by the propensity score, e.g. smoking status
    - Not intuitive that ADT would be associated with more DM, but less risk for cardiovascular morbidity and mortality. The length of follow up, however, may not have allowed adequate time to capture the full impact of a new diagnosis of DM on cardiovascular health
    - Results with respect to fracture risk in keeping with previous studies

- Bottom line for Canadian Medical Oncologists:
    - This study contributes to the evidence that new onset of DM should be included among the known list of potential adverse effects of ADT, all of which must be considered in the context of a patient's disease aggressiveness, competing co-morbidities, age and frailty when making ADT treatment decisions
    - Balancing cancer control and quality of life may be achieved by deciding not to use ADT in some cases, or limiting exposure in others (e.g. intermittent ADT with treatment breaks during which testosterone is allowed to rise)
    - This study can may further reassure patients/physicians who had concerns related to a potential for increased risk for cardiovascular disease with ADT