Cardiovascular Mortality following Short-term Androgen Deprivation in Clinically Localized Prostate Cancer: An Analysis of RTOG 94-08

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Background

- Androgen deprivation therapy (ADT) has been shown to increase risk for metabolic syndrome, cardiovascular disease (CVD) up to 16% and diabetes (DM) up to 40% (Keating JCO 2006).
- It is unclear what is the impact of CVD related mortality in patients treated with ADT, especially in groups where risk for prostate cancer related mortality may be low and the benefit for ADT may not be substantial enough to the increase the risk of CVD mortality.
- To clarify the above question, authors of this study, evaluated ADT related mortality in men treated with radiation with/without ADT in RTOG 94-08.

Methods

- 1979 patients with T1-2, PSA<20 were randomized to radiation alone or radiation + 4 months of ADT from 1994-2001.
- Hazards ratio were calculated to compare disease specific and CVD mortality in the two groups.
- Multivariate analysis (MVA) was performed to evaluate risk for CVD mortality. Covariates include were: PSA, GS, T stage, age, race, weight, history of CVD, DM, and hypertension (HTN)

Results

- Patients were well balanced in the two groups (age, disease features and baseline CVD risk factors such as DM and HTN) except that there were slightly higher numbers of patients with pervious history of CVD in the RT+ADT group. 90% of all patients had low or intermediate risk prostate cancer.
- With median follow up of 8.2 years, there were 191 CVD deaths. There were 10.7% cardiovascular related deaths in RT group vs 9.8% in RT+ADT group at 10 years. Essentially similar rates of CVD related mortality in the two groups.
- As previously reported, there was improved DFS and OS in the RT+ADT group in RTOG 94-08 (Jones, NEJM 2011).
- On MVA, only history of prior CVD (HR 2.94, p=<0.001) and DM (HR 1.51, p=<0.03) were associated with increased CVD mortality. Use of ADT with treatment was not a significant predictor of CVD related death.
- There was no difference in CVD mortality in patients with high risk of CVD (age 70 or older and baseline CVD or DM) vs patients with low risk of CVD.
- Number need to harm was >380 patients treated with ADT per MI. Number need to treat with ADT was 17 per life saved from prostate cancer death.

Conclusions

- ADT doesn't seem to increase risk of CVD mortality in men with clinically localized prostate cancer. However, it has shown to improve DFS and OS especially in intermediate risk patients.
- These results are confirmed in the meta-analysis recently presented by Nguyen et al (ASTRO, 2011 #10).
• Possible reason for not seeing increased risk of CVD in patients on ADT is that GnRH agonists have mixed impact on CVD risk factors, such as increasing HDL (which is protective against cardiovascular events), increasing LDL, weight and insulin resistance and no impact or CRP and blood pressure.

• Having said that 30% of patients in this study died of CVD, which presents an opportunity for educating our patients about metabolic syndrome and benefits of leading an active, healthy lifestyle.

Clinical and Scientific Implications

This presentation adds important information in the era of combined hormonal therapy and radiation therapy. ADT is not a major contributor to CVD mortality in this group of patients as previously considered. In light of this paper and the meta-analysis presented earlier in the meeting, it is clear that ADT is not associated with significantly higher risk of CVD mortality. Risk factors of CVD remain the same—DM and prior history of CVD, which should be addressed in this population just as all other non-prostate cancer patients with metabolic risk factors.