A multicenter phase III comparison of docetaxel + prednisone and mitoxantrone + prednisone in patients with hormone-refractory prostate cancer

This article discusses non-FDA approved dosing of docetaxel **Presenter:** M.A. Eisenberger

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Type of Session: Plenary

Background

- Therapy for metastatic hormone-refractory prostate cancer (HRPC) has usually consisted of chemotherapy, with studies showing response rates as high as 40-50%
- The standard chemotherapy treatment for HRPC is mitoxantrone (MTZ) + prednisone (P) which has been shown to improve palliation in these patients, but has not been shown to improve overall survival
- In an effort to increase response rates, additional chemotherapeutic agents such as taxanes have been studied and shown to increase response in pilot studies
- This study was undertaken to examine if treatment with docetaxel (D) + P leads to improved responses and survival compared to the standard therapy of MTZ + P

Materials and Methods

- Patients with metastatic androgen independent prostate cancer who had undergone orchiectomy and/or LHRH agonist treatment who had testosterone levels <=50 ng/DL and progressive disease were enrolled
- Patients were excluded if they had prior chemotherapy and pain scores and analgesic requirements that were not stable
- Patients were randomized to one of three arms:
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  - D q3wk Arm: D (75 mg/m2 q3wk) + P (5 mg bid)
  - D qwk Arm: D (30 mg/m2 qwk foir 5/6 wks) + P (5 mg bid)
  - MTZ Arm: MTZ (12 mg/m2 q3wk) + P (5 mg bid)
  - All three arms had a total treatment duration of 30 wks
- Gondal suppression was maintained during treatment
- Estramustine, antiandrogens, estrogens, and progestins were discontinued 4-6 wks prior to initiation of the study therapy
- Patients were stratified by pain score and analgesic requirements and by Karnofsky Performance Status (KPS)

Results

- A total of 1006 patients were enrolled on the study
- Median follow-up = 20.7 mo
- Patient groups were well balanced for age, KPS, and pain level/analgesia requirements
- Patients in the D qwk arm were more likely to have undergone radical prostatectomy (19% vs. 52% (D q3wk) vs. 21% (MTZ))
- Median survival was improved for both of the docetaxel arms:
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    - D q3wk: 18.9 mo, hazard ratio (HR) = 0.76, p = 0.009
    - D qwk: 17.3 mo, HR = 0.82, p = 0.03
    - MTZ: 16.4 mo
- HR for death = 0.76 (95% CI 0.62-0.94) with the addition of docetaxel
- The docetaxel arms had greater decrease in PSA compared to MTZ (45% vs. 32%)
- Patients differed in their likelihood of completing therapy: 46% (D q3wk) vs. 35% (D qwk) vs. 25% (MTZ)
- More patients on the MTZ Arm experienced disease progression: 38% (D q3wk) vs. 35% (D qwk) vs. 56% (MTZ)
- More patients on the D qwk Arm experience adverse events: 11% (D q3wk) vs. 16% (D qwk) vs. 10% (MTZ)
- Patients on the D qwk Arm experienced significantly less grade 3/4 neutropenia: 32% (D q3wk) vs. 1.5% (D qwk) vs. 22% (MTZ)
- There was no difference in the rates of neutropenic fevers or infections, and the overall rates of these events was low
- Pain response was improved for D q3wk (p=0.01) but not D qwk (p=0.07)
- FACT-P (pain) QOL scale was improved for both D q3wk (p=0.009) and for D qwk (p=0.005)

Author's Conclusions

- The use of docetaxel in HRPC is safe and increases survival by 24%
- Docetaxel improves PSA response and improves pain scores
- Prostate cancer should now be considered a chemotherapy sensitive disease
- Docetaxel with prednisone is the new standard of care in treatment of HRPC
- Future studies should address the role of docetaxel in earlier stage prostate cancer

Clinical/Scientific Implications

This study in conjunction with SWOG 9916 (which was also present during this plenary session) both show a survival benefit with the use of docetaxel in the setting of HRPC. This is the first time that an overall survival benefit has been seen with the addition of chemotherapy in these patients. It should be noted that although the survival benefit was statistically significant in both studies, the overall gain was small. The use of docetaxel q3wk resulted in an increase in median survival of only 2 months. When compared to SWOG 9916, both studies showed similar rates of PSA response, objective response, median survival, and hazard ratio for death compared to MTX + P. With these two studies, it appears clear that docetaxel is an active agent with disease. The optimal scheduling of docetaxel is still unclear. Although the D q3wk arm achieved a higher median survival, it was also associated with higher rates of grade 3/4 neutropenia. The study was not powered to directly compare these two arms; therefore, a definitive conclusion regarding docetaxel scheduling cannot be drawn. What is clear is that although docetaxel is active, its overall benefit is modest. Future studies utilizing docetaxel with other agents should be studied

in an attempt to increase the overall benefit seen with chemotherapy. More importantly, these two studies (TAX-327 and SWOG 9916) may help change to prevalent mentality that prostate cancer is a chemotherapy resistant disease.

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