SWOG 99-16: Randomized phase III trial of docetaxel (D)/estramustine (E) versus mitoxantrone (M)/prednisone (P) in men with androgen-independent prostate cancer (AIPCA)

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Background

The present-day standard of care in the treatment of AIPCA patients consists of the combination of mitoxantrone and prednisone for palliation of disease-related symptoms. There is no remarkable survival benefit with the use of these agents, and thus the ultimate prognosis of this patient group has remained dismal. Given this large roadblock in the treatment of AIPCA, attempts to define effective chemotherapeutic regimens that might help overcome this block are of particular clinical interest. Preclinical data have demonstrated a trend towards improved median survival with the combination of docetaxel and estramustine (Petrylak et al. JCO 17(3), 1999). This large intergroup collaboration was initiated in order to further examine the efficacy of D+E compared to the standard regimen of M+P in a randomized, phase III setting.

Materials and Methods

- 770 men with AIPCA were accrued between 10/1999 and 1/2003
- Participating institutions included SWOG, CALGB, NCCTG, CTSU, NCI
- Eligible patients had the following criteria: progressive disease despite surgical and/or medical castration; progressive disease following anti-androgen treatment withdrawal; adequate renal and hepatic function; SWOG performance status of 0-3; and prior treatment with no more than one non-taxane, non-estramustine, non-anthracycline chemotherapy agent.
- Progressive disease was defined in one of 3 ways, and patients were stratified based on a+b versus c:
  - a) bi-dimensionally measurable lesion growth
  - b) evaluable but not measurable progression (ie: bone scan progression)
  - c) rising serum PSA level with 2 consecutive rises (biochemical)
- Patients were not allowed to have brain metastases, history of anticoagulation use, or surgery/bisphosphonates/radiation/chemotherapy within 30 days of enrolment
- Patients were randomized to one of two arms:
1) D+E: docetaxel 60 mg/m2 IV on day 2, every 21 days + estramustine 280 mg po tid days 1-5 (n=334)
2) M+P: mitoxantrone 12 mg/m2 IV every 21 days + prednisone 5 mg po bid continuously (n=332)
Both arms were well-balanced for patient characteristics, with both arms having a median age of 70 years old and a ~20% rate of patients with biochemical progression only.

Primary endpoint was overall survival (OS)
Secondary endpoints were progression-free survival (PFS), objective response rate (ORR), and rate of >50% PSA decline
Final analysis was performed 2/2004, with all one-sided p values.

Of note:
- dose escalation of docetaxel to 70 mg/m2 was permitted if no toxicity was seen on 60 mg/m2.
- prophylactic anticoagulation was permitted on the D+E arm after 1/2001 secondary to higher rate of deep venous thrombotic events

Results
- The results reported here are all for arm 1 (D+E) versus arm 2 (M+P).
- Median overall survival was 18 months vs. 16 months, with a hazard ratio (HR) of 0.80, p=0.01
- PFS was 6 months vs. 3 months, HR = 0.73, p<0.0001
- The ORR was 17% (n=103) vs. 11% (n=93), p=0.15
- The rate of patients with >50% PSA decline was 50% vs. 27%, p<0.0001
- Grade 3/4 toxicity was higher in the D+E arm for the following adverse effects: pain, neuropathy, infection, metabolic derangements, gastrointestinal complications, and cardiovascular/thromboembolic complications.
- Despite this, there was NO increased rate of toxic deaths or withdrawal from therapy for excessive toxicity in the D+E arm.

Author's Conclusions
- There was a 20% reduction in risk of death in the D+E arm compared to standard M+P.
- There was a 27% improvement in PFS in the D+E arm compared to standard M+P.
- There was an increased number of patients with PSA decline of >50% from baseline (50% vs. 27%).
- There was a trend towards improved objective response rate in the D+E arm.
- Although there was greater grade 3/4 toxicity, the rates of toxic deaths or study discontinuation did not differ.
- D+E should now become the new reference regimen defining standard of care in the treatment of AIPCA.

Clinical/Scientific Implications
This year, two very pivotal studies have emerged regarding the optimal management of AIPCA patients. The study discussed here demonstrates the superiority of docetaxel and estramustine chemotherapy on survival and objective response as compared to the current standard of mitoxantrone and prednisone. The achievement of a survival benefit in this well-designed intergroup trial is revolutionary in terms of changing the paradigm of clinical AIPCA management. Firstly, this is the first large randomized study to detect a survival advantage in this group of patients that previously was "resigned" to receive palliative
therapy with "soft", subjective endpoints. While the goal of alleviating patients' pain and obtaining subjective, symptomatic relief is certainly important, the results presented here encourage clinicians to reach for higher, more objective goals, namely improved survival.

Though modest (lengthened survival by ~2-2.5 months), the benefits with D+E are statistically significant and warrant further investigation in this area. Most of the higher grade 3/4 toxicity noted with this arm is attributed to the estramustine component of this doublet. The results of the European/Canadian TAX 327 trial, also presented at ASCO this year, show survival gains with the use of docetaxel monotherapy that are very comparable to those achieved here with docetaxel and estramustine. Given this fact, together with the higher rate of grade 3/4 toxicity seen because of the estramustine, some clinicians might make a valid argument for the omission of estramustine altogether. Future studies are likely to incorporate this hypothesis of docetaxel being the truly active agent, and the estramustine being unnecessary. In addition, several trials are ongoing and have been presented at ASCO this year on the use of docetaxel in conjunction with other non-chemotherapeutic agents, such as celecoxib, imatinib, etc.

The results from this study are likely to have a considerable impact on the referral and practice patterns of urologists in the US. Whereas patients with AIPCA might have traditionally undergone multiple trials of hormonal therapy, with only about 25% of them eventually being referred for chemotherapy, the data shown may very well alter that practice in the future. The old perception of AIPCA as a non-chemotherapy problem may slowly be replaced with one of a chemosensitive disease.

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