Prostate cancer

ADJUVANT CHEMOTHERAPY IN HIGH-RISK PROSTATE CANCER

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TRIAL SUMMARY: Overall survival improved with docetaxel

Sandler HM et al. A phase III protocol of androgen suppression (AS) and radiotherapy (RT) vs AS and RT followed by chemotherapy with docetaxel and prednisone for localized, high-risk prostate cancer. 2015 American Society of Clinical Oncology Annual meeting, Clin Oncol 33, 2015 (suppl; abstrLBa5002).

In the RTOG 0521 study, patients with localized, non-metastatic, high-risk prostate cancer were randomized to androgen suppression (AS) + radiotherapy (RT) vs AS+RT followed by chemotherapy (CT) with docetaxel and prednison. High-risk prostate cancer categories were defined as: 1) Gleason (GL) 7–8, any T-stage, and prostate-specific antigen (PSA) ≥20, or 2) GL 8, ≥T2, any PSA, or 3) GL 9–10, any T-stage, any PSA. All PSA are ≤150. RT dose was 72.0–75.6 Gy. AS includes luteinizing hormone-releasing hormone (LHRH) agonist for 24 months beginning 8 weeks before RT and oral antiandrogen through to the end of RT. CT consisted of 6 21-day cycles of docetaxel 75 mg/m² + prednison 10 mg daily beginning 4 weeks after RT. The study was designed to detect improvement in 4-year overall survival (OS) from 86% to 93% with 51% hazard reduction (HR=0.49). With P-value of 0.05 and 90% power, at least 78 deaths were required to analyze the OS endpoint. A total of 563 patients were evaluable for analysis. Their median age was 66 years and median PSA was 15 ng/mL. They were stratified according to the risk category, and 53% had GL 9–10, 27% had cT3–4 and 33% were pN0.

Results: After a median followup of 6 years, the 4-year OS was 89% for AS+RT arm, and 93% for the AS+RT+CT arm, p=0.04 (HR 0.70, 90% CI: 0.51–0.98). The 6-year disease-free survival (DFS) was 65% for AS+RT and 55% for AS+RT+CT, p=0.04 (HR 0.76, 95% CI: 0.58–0.99). Distant metastasis was reduced in the chemotherapy arm with 41 events in AS+RT and 26 events in AS+RT+CT, p=0.05. Grade 3 and 4 adverse events (AE) were, as expected, higher in the chemotherapy arm with 38% grade 3 and 26% grade 4 AEs compared to 21% grade 3 and 1% grade 4 AEs in the control arm. These were primarily hematologic events. RT was delivered as per protocol in 95%, CT was delivered in 86% (82% without modification or delays), 100% and 98% had received LHRH agonist and oral antiandrogen, respectively.

COMMENTARY: Patients with locally advanced or high-risk localized prostate cancer have a relatively poor prognosis. Standard management often involves RT and long-term (2–3 years) hormonal therapy. Chemotherapy (docetaxel) has been shown to be beneficial in metastatic, castration-resistant prostate cancer. More recently, in the CHAARTED trial, the combination of chemotherapy and hormonal therapy in hormone-naive extensive disease has significantly improved survival compared with ADT alone (HR=0.61, 95% CI: 0.47–0.80). Preliminary results from the STAMPEDE study were presented at ASCO 2015 and showed a marked survival benefit from adding docetaxel to standard of care (SOC) ADT+/–RT for patients with metastatic or locally advanced/ localized hormone-naive prostate cancer compared with SOC alone (HR=0.76, 95% CI:0.63–0.91, p=0.003).

In the present RTOG 0521 study, adjuvant docetaxel and prednisone after RT and AS improved 4-year OS compared with RT and AS alone (93% vs 89%), p=0.04 (1-sided HR 0.70, 90% CI: 0.51–0.98). It showed improved DFS with a 10% absolute difference at 6 years favouring the docetaxel arm. Distant metastases were also reduced, with 26 events in docetaxel and 41 in the other arm. Toxicity was higher in the chemotherapy group, with 2 deaths, and involved mainly hematologic events. These relatively early results with a short OS assessment period suggest a potential role for docetaxel in hormone-sensitive prostate cancer. In their oral presentation at ASCO, the authors described the one-sided log rank and 90% power as potential weaknesses in the

IN BRIEF

Already known

• Docetaxel significantly improves overall survival (OS) in metastatic castration-resistant prostate cancer (mCRPC) and in high-volume metastatic hormone naïve prostate cancer (PCa) with metastatic disease diagnosed upfront or soon after initial local treatment.

What this study showed

• Adjuvant docetaxel and prednisone after RT and androgen suppression demonstrated a 10% benefit in disease-free survival at 6 years in high-risk nonmetastatic PCa.

Next steps

• Further assess the role for docetaxel in nonmetastatic, high-risk hormone-sensitive prostate cancer with longer followup on OS.
study. While the study did not meet the planned primary objective of HR=0.49 for OS, we can recognize that as an especially ambitious target. Initial results of the GETUG12 trial analyzing the role of docetaxel combined with estramustine in high-risk prostate cancer also demonstrated improved DFS but does not yet have mature OS. Additional followup is warranted to determine long-term benefits of docetaxel in localized high-risk disease.

References:
1. Sweeney CJ et al, ChemoHormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer, E3805 CHAARTED trial, J Clin Oncol 32:5s, 2014 (suppl; abstract LBA2)
2. James ND et al, Docetaxel and/or zoledronic acid for hormone-naive prostate cancer, STAMPEDE trial, J Clin Oncol 33, 2015 (suppl; abstract 5001)