Chemotherapy research for metastatic prostate cancer

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Cite as: *Can Urol Assoc J* 2016;10(7-8-Suppl3):S140-3 http://dx.doi.org/10.5489/cuaj.4055

Declines in quality of life with early docetaxel treatment may be offset by long-term gains for men with metastatic hormone-sensitive prostate cancer

In 2004, docetaxel was recognized as the first agent to confer an overall survival (OS) benefit in men with metastatic prostate cancer;[1,2] however, docetaxel is also associated with known side effects that can diminish quality of life (QOL).[3,4] The CHAARTED study, which showed an OS benefit of docetaxel in metastatic, hormone-sensitive prostate cancer,[5] also included global measures of QOL that account for disease-related symptoms, as well as treatment-related symptoms. Dr. Linda Patrick-Miller presented the QOL results from CHAARTED at ASCO 2016.[6] The 790 patients in CHAARTED who were randomly assigned to androgen-deprivation therapy (ADT) plus docetaxel (n=397) or ADT alone (n=393) underwent QOL assessment at baseline, three, six, nine, and 12 months following randomization. Compared with those who received ADT alone, the patients who received the combination of ADT plus docetaxel had significantly worse overall QOL, as measured by Functional Assessment of Cancer Therapy-Prostate (FACT-P) scores, at three months (p=0.02); however, by Month 12, their FACT-P scores were significantly better (p=0.04). As expected, fatigue was significantly worse at three months in the docetaxel group, as measured by Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scores (p<0.001); however, by six months, FACIT-F scores had returned to baseline and were no different from those who received ADT alone. FACT-Taxane scores were significantly worse in the docetaxel group at all time points, but Brief Pain Inventory (BPI) scores did not differ between the two groups at any time. Emotional well-being was significantly greater in the docetaxel group at all time points. Coupled with the OS benefit observed in metastatic hormone-sensitive prostate cancer, these results suggest that early docetaxel treatment offers a clinically meaningful benefit in men with newly diagnosed advanced prostate cancer.

Intermittent docetaxel is non-inferior to continuous docetaxel treatment in one-year survival of men with metastatic castrate-resistant prostate cancer.

Intermittent docetaxel treatment offers patients the benefit of a "treatment holiday" — reducing their overall exposure to docetaxel and cumulative toxicity, and potentially delaying resistance to taxanes.[7] However, data on the non-inferiority of intermittent vs. continuous docetaxel in men with castrate-resistant prostate cancer (CRPC) are lacking. The PRINCE study randomly assigned men with chemotherapy-naïve metastatic CRPC (mCRPC) to either intermittent (n=78) or continuous (n=78) treatment with docetaxel.[8] Men in the intermittent treatment arm were started on a 12-week sequence of either four cycles given in a three-weekly regimen or three cycles in a weekly regimen, followed by a treatment holiday until disease progression. The continuous arm received docetaxel in either a three-weekly or weekly regimen until death. Patients in the intermittent arm spent a median time of 15 weeks on a treatment holiday (range 1–69 weeks), translating to 38% of the overall treatment duration. One-year survival was similar between the intermittent and continuous treatment arms (75.8% vs. 72.6%) and met the non-inferiority criteria. However, the difference in median OS (18.3 months vs. 19.3 months) did not meet the non-inferiority criteria, according to a post-hoc analysis. Differences in progression-free survival (PFS) and time to treatment failure were not significant between the two groups and the safety profiles of both study arms were comparable. The PRINCE study was limited by poor recruitment, resulting in a power of only 39% of the planned study. Although results of a study with such a small sample size cannot be used to determine whether intermittent docetaxel is truly non-inferior to continuous treatment, these results still suggest that intermittent docetaxel may present a treatment option for patients with mCRPC.

Cabazitaxel trials presented at ASCO 2016 show similar overall survival to docetaxel and maintenance of survival benefits with lower dose

The phase 3 TROPIC study showed that cabazitaxel plus prednisone significantly improves OS in men with mCRPC who have previously been treated with a docetaxel-containing regimen compared with mitoxantrone plus prednisone.[9] Building on these results, the multinational, open-label, phase 3 FIRSTANA study examined whether cabazitaxel plus prednisone is superior to docetaxel plus prednisone in chemotherapy-naïve mCRPC.[10] The first trial to compare two life-prolonging therapies in mCRPC, FIRSTANA enrolled patients with mCRPC and Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 who had progressed after castration. Patients were randomly assigned in 1:1:1 ratio to cabazitaxel 20 mg/m^2 every three weeks (n=391), cabazitaxel 25 mg/m^2 every three weeks (n=389), or docetaxel 75 mg/m^2 (n=388) — all given every three weeks with prednisone 10 mg/day.

Median OS, the primary endpoint of the study, did not differ among the three groups (24.5 months for cabazitaxel 20 mg/m^2, 25.2 months for cabazitaxel 25 mg/m^2, and 24.3 months for docetaxel 75 mg/m^2) (Fig. 1). The secondary endpoint PFS (based on tumour, prostate-specific antigen [PSA], pain progression, or death) also did not differ significantly among the three groups (4.4 months for cabazitaxel 20 mg/m^2, 5.1 months for cabazitaxel 25 mg/m^2, and 5.3 months for docetaxel 75 mg/m^2). The Response Evaluation Criteria In Solid Tumours (RECIST) response rate was significantly better in the cabazitaxel 25 mg/m^2 group than in the docetaxel 75 mg/m^2 group (41.6% vs. 30.9%; p=0.0370). Other secondary endpoints, including PSA response rate, did not significantly differ across groups.

While no new safety concerns were identified, differences in toxicity profiles among the taxanes were noted. Treatment-emergent adverse events (TEAEs) were less frequent across most categories in the cabazitaxel 20 mg/m^2 group. Febrile neutropenia, diarrhea, and hematuria were more frequent in men treated with cabazitaxel 25 mg/m^2, while peripheral neuropathy, peripheral edema, alopecia, and nail disorders were more frequent in men treated with docetaxel.

Determining the right dose for the right patient remains a significant challenge for many drugs used in oncology today, including cabazitaxel. Results of the open-label PROSELICA study, exploring the inferiority of a slightly lower dose of cabazitaxel, 20 mg/m^2, were presented by de Bono and colleagues at ASCO 2016.[11] This multinational, phase 3 study involved 1200 men with mCRPC and ECOG performance status 0–2, who had progressed after treatment with docetaxel. The men were randomly assigned in a 1:1 ratio to either 20 mg/m^2 or 25 mg/m^2 of cabazitaxel plus prednisone, with the hypothesis that the 20 mg/m^2 dose would

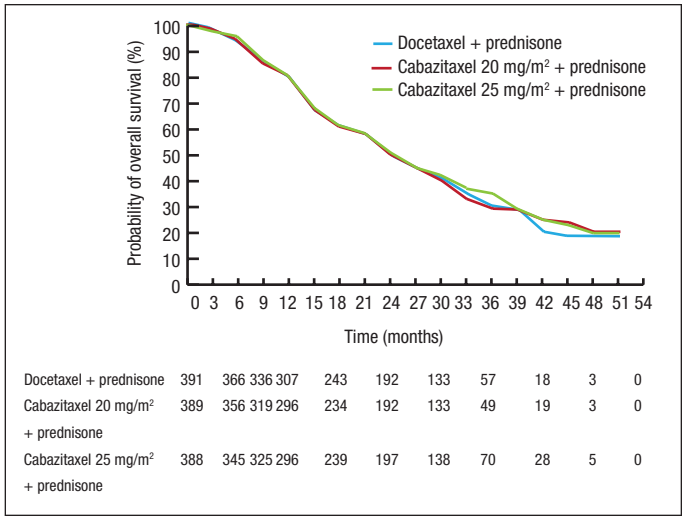

Fig.1. Overall survival in the FIRSTANA trial.[10]

maintain at least 50% of the OS benefit of the 25 mg/m^2 dose relative to mitoxantrone observed in the TROPIC trial. The higher dose did not necessitate a lower delivered dose intensity (median 0.99 vs. 0.98) or decrease in the number of cycles administered (7 vs. 6) compared with the lower dose. However, more patients in the higher-dose group had a dose reduction by 1 (21.5% vs. 10%). Very few patients in either arm had a second dose reduction. With a median OS of 13.4 vs. 14.5 months in the lower vs. higher dose groups (hazard ratio [HR] 1.024), the one-side 98.9% upper-bound confidence interval [CI] of 1.184 was within the non-inferiority margin of 1.214. Of interest, in the subgroup of patients who had prior treatment with either abiraterone or enzalutamide, there was a trend toward improved survival with the higher dose of cabazitaxel; however, these differences did not reach statistical significance and the data are purely hypothesis-generating. There was no difference in PFS. The higher dose of cabazitaxel did result in a higher PSA response rate (42.9% vs. 29.5%; p<0.0001) and a trend toward a higher RECIST response rate (23.4% vs. 18.5%; p=0.1924), but was also associated with a higher rate of Grade 3–4 TEAEs than the lower dose, including higher rates of febrile neutropenia, hematuria, and diarrhea.

TAXYNERGY trial shows that early taxane switch may improve PSA response rate and that androgen receptor nuclear localization may indicate taxane sensitivity/resistance

In men with advanced prostate cancer, PSA declines with chemotherapy are associated with a survival advantage;[12,13] however, approximately half of men with CRPC do not achieve PSA declines of 50% or greater with taxane-based chemotherapy.[12] Because taxanes are not completely cross-resistant,[9,14] the randomized phase 2 TAXYNERGY trial explored whether an early taxane switch would benefit men

who failed to achieve a sufficient PSA decline within four cycles of their original taxane therapy.[15] A total of 63 men with chemotherapy-naïve mCRPC were randomly assigned in a 2:1 ratio to first-line docetaxel (n=41) or cabazitaxel (n=22) and switched to the other taxane if their PSA did not decline by 30% or more by the fourth cycle. Otherwise, they remained on their original chemotherapy. Treatment was continued until progression, unacceptable toxicity, investigator decision, or study cut-off. Nearly one-third (29.3%) of those who received first-line docetaxel and 13.6% of those who received first-line cabazitaxel did not achieve PSA declines of 30% or greater by Cycle 4 and were, therefore, switched to the alternative taxane. By study end, 55.6% of the overall population achieved a PSA response of 50% or greater; the predefined lower limit of 10% of the one-sided CI was 47.5%, which exceeded the historical control rate of 45.4% and was, therefore, positive.

The study also evaluated the association of biomarkers with taxane response/resistance by collecting circulating tumour cells (CTCs) at multiple time points — representing a real-time opportunity to investigate the mechanism of action (MOA) of taxanes. Analysis of CTCs for androgen receptor nuclear localization (ARNL) revealed that patients who experienced a 50% or greater decline in PSA had a mean decrease in ARNL of 6.5%, compared with an increase of 6.1% in those who did not achieve a 50% PSA decline (p=0.03). These results from TAXYNERGY suggest that further studies are warranted to identify the men with metastatic prostate cancer who might benefit from an early switch in taxane treatment. ARNL was identified as a potential marker of taxane sensitivity/resistance, which is consistent with the proposed MOA. Although interesting, these results should not yet change the way we routinely manage our patients with mCRPC who receive taxanes.

Docetaxel monotherapy may generate a more rapid biochemical progression after radical prostatectomy in patients with Gleason score 7 or lower

Docetaxel has been shown to prolong survival in a number of advanced cancers, including breast, colorectal, and prostate cancer. In breast and colorectal cancer, a survival benefit has also been shown for docetaxel in the adjuvant setting. The multinational open-label phase 3 SPCG12 trial sought to determine whether a similar benefit would be seen for adjuvant docetaxel monotherapy in advanced prostate cancer.[16] Following radical prostatectomy, 459 men with high-risk prostate cancer were randomly assigned to receive either six cycles of adjuvant docetaxel 75 mg/m^2 every three weeks (in the absence of continuous steroids or ADT) for six weeks, or surveillance until their PSA levels reached 0.5 ng/mL. A higher than expected 14.2% rate of febrile neutropenia was observed, which may have been due to the lack of concomitant hormonal therapy and/or the recent surgery, creating a higher risk of infection. Biochemical progression, defined as a PSA level higher than 0.5 ng/mL, was seen in 41.8% of the overall intent-to-treat population, with a trend toward greater progression in the docetaxel arm than in the surveillance arm (44.8% vs. 38.9%; p=0.078). Initially, the docetaxel arm saw a very low rate of progression; however, once docetaxel was stopped there was an increased rate of progression in the docetaxel arm compared with the surveillance arm, with the two curves crossing at 15 months. Beyond 24 months, the biochemical-free survival was consistently 10% lower in the docetaxel arm than in the surveillance arm (Fig. 2).

The strongest prognostic factors for biochemical progression were Gleason score of 8 or higher and lymph node metastases. Interestingly, the subgroup of patients with a Gleason score of 7 or lower fared significantly better with surveillance than with docetaxel monotherapy (HR 1.61) and there was a similar trend in the subgroup of patients with no lymph node metastases (HR 1.33). Overall, this study failed to prove the hypothesis that adjuvant docetaxel following radical prostatectomy provides a biochemical PFS advantage in men with high-risk prostate cancer. Instead, certain subgroups may actually fare better with active surveillance. The results of this study contrast those of the three previously reported post-radiation adjuvant studies that all showed an improvement in recurrence-free survival and immature OS estimates.[17-19] Other than the local treatment modality used, the only major differences between this study and the other four is the lack of ADT used in the Scandinavian post-surgical study. More studies are needed to fully understand the role (if any) of chemotherapy in this population.

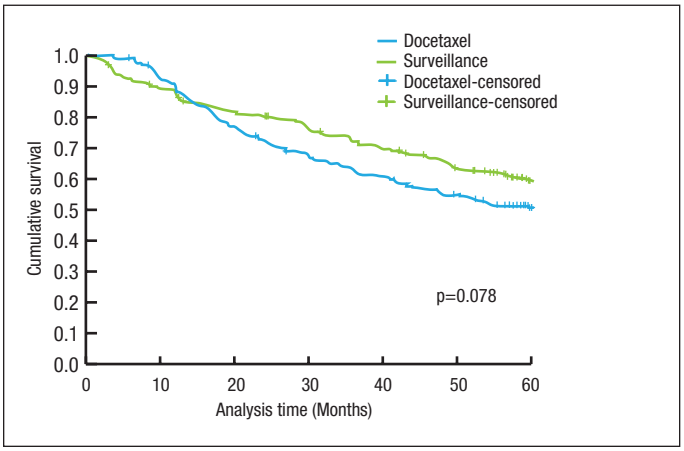

Fig. 2. Biochemical progression-free survival of patients randomly assigned to docetaxel monotherapy or surveillance following radical prostatectomy.[16]

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