Cancer Biology & Therapy 16:1, 17–18; January 2015; © 2015 Taylor & Francis Group, LLC

2-weekly docetaxel: issues for clinical practice

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In the phase III trial comparing 2 docetaxel schedules (3-weekly versus 2-weekly) as first-line chemotherapy for CRPC, recently published in *The Lancet Oncology*, fewer serious adverse events, particularly hematologic toxicities, and longer times on treatment, in favor of the 2-weekly regimen are reported.[1,2,3]

The trial was aimed to provide concrete answers to a series of issues involving the clinical practice and concerning the toxicity profile of a standard treatment, which is offered to elderly or unfit patients.

Nevertheless, the primary objective of the study was to demonstrate a difference in terms of time to treatment failure (TTTF), which was defined as time from randomization to treatment discontinuation for any reason, including disease progression, toxicity or death. A statistically significant advantage in favor of the experimental schedule was found, not only in TTTF (5.6 vs. 4.9 months; $p = 0.014$) but also in time to progression and OS (19.5 versus 17 months, $p = 0.021$), although the study was not powered to assess this latest difference. These data deserve in our opinion few considerations.

Given that the trial was originally designed and powered to determine a significant advantage in TTTF of 2 months overall (from 5 to 7 months), the primary end-point should be considered actually unmet, although the difference reaches the statistical significance. Besides, we agree that clinical practice should be guided on the basis of reliable evidences but a compromise taking into account the difficulties in conducting randomized trials and the needs of treating patients on the clinical practice basis, may soften the crude interpretation of results. Thus, this schedule could be preferred perhaps for the tolerability, although it seems surprising that a treatment with less hematologic toxicities led to a double dilation rate (10% vs. 5%).

Given that only 20% of patients in both arms received second line treatment, the significant differences in OS, may be hypothetically explained by the higher median total cumulative dose in the experimental arm (600 versus 450 mg/m^2).

With regard to the low rate of patients with PS 2 in both arms (6%) and the lack of data concerning the comorbidities, the conclusions about the use of the experimental schedule for unfit patients, or those unsuitable for large single doses of docetaxel should be considered cautiously.

With regard to the treatment duration, the significant higher percentage of doses-delay in the 2-weekly group may be considered the more significant contributor to the longer TTTF, rather than the overall treatment's duration.

Unfortunately, because of the low proportion of patients receiving second line therapy in the study may be difficult to translate the reported results into clinical practice.

Moreover, we have evidences that prolonging the first-line treatment may not be the best choice in CRPC, given the good response rate to docetaxel re-challenge in responding patients[4,5] and the improved OS obtained with the introduction in clinical practice of abiraterone,[6] cabazitaxel[7] and enzalutamide.[8]

At the last ASCO Annual Meeting, Dr. Sweeney presented results of the E3805 trial, titled Chemohormonal Therapy vs. Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED)[9]. The trial compared "upfront" chemotherapy plus androgen deprivation therapy (ADT) to

Keywords: mCRPC, doxetaxel, 3-weekly schedule

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Submitted: 09/19/2014

Revised: 10/21/2014

Accepted: 11/09/2014

http://dx.doi.org/10.4161/15384047.2014.987534

ADT alone in men with metastatic prostate cancer: median OS was 57.6 months in the ADT plus docetaxel arm and 44.0 months in the ADT arm (hazard ratio [HR] 0.61, 95% CI [0.47, 0.80]; p = 0.0003). In men with high-volume disease, median OS was 49.2 months with docetaxel plus ADT compared with 32.2 months with ADT, a difference of 17 months (HR 0.60, 95% CI [0.45, 0.81]; p = 0.0006). In men with low-volume disease, median OS had not been reached at the time of the analysis. This trial could probably change the use of docetaxel in clinical practice in patients with metastic prostate cancer.

In addition, we should limit the magnitude of these data to the caucasian population and the northern european countries, given we cannot rule the impact of demographics upon this comparison.

In conclusion, despite the originality of the trial and the effort to offer a therapeutic option for patients not amenable to the standard schedule, the above reported issues should be carefully considered, before translating these results in clinical practice.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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