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Continuous versus intermittent docetaxel for metastatic castration resistant prostate cancer

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ABSTRACT

Docetaxel (DTX) is a standard chemotherapeutic agent for metastatic castration resistant prostate cancer (mCRPC). However, given a number of toxicities associated with DTX, considerable debate exists regarding the optimal number of DTX cycles to be administered in this setting. In clinic, it is a usual practice to continue DTX until toxicities or disease progression precludes its administration. Therefore, we undertook a comprehensive review of the literature on intermittent versus continuous chemotherapy administration in this setting. Although there is no head-to-head comparison of these two approaches, our review discovered many studies which show that intermittent approach is a very feasible and attractive option with lower toxicities and better quality of life. Because of the availability of many newer agents that can be used post-docetaxel, stopping DTX early seems to be more appropriate with introduction of docetaxel or newer agents upon progression. This review summarizes the data from available studies regarding the feasibility and controversies of intermittent docetaxel in prostate cancer.

1. Background

Prostate cancer is one of the most common and lethal malignancies among men. The recent statistics show that prostate cancer alone will account for a quarter of new cancer diagnosis in men in the United States in 2015. It will also be the second leading cause for cancer deaths in the year 2015 (Siegel et al., 2015). Although localized prostate cancer can be cured with surgery and/or radiation therapy, around 10–20% of the patients present with metastatic disease and many patients with localized disease relapse with metastasis (Tannock et al., 2004). This advanced disease, though initially sensitive to androgen ablation, eventually becomes resistant to androgen deprivation and continues to progress despite castrate level of androgen deprivation. This is known as metastatic cas-

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tration resistant prostate cancer (mCRPC) and represents a major challenge in genitourinary oncology. Docetaxel (DTX) is the standard chemotherapeutic agent of choice in the management of mCRPC, however consensus lacks regarding whether continuous DTX represents any benefit over stopping it after a fixed number of cycles, the so-called intermittent approach. In this paper, we provide a comprehensive and up-to-date review of the available evidence on DTX use in mCRPC.

2. Chemotherapy in mCRPC

Mitoxantrone was the first chemotherapy agent to show a positive result in the setting of mCRPC. It improved pain and quality of life (QoL) but showed no survival benefit (Tannock et al., 1996). In 2004, two simultaneously published papers in the *New England Journal of Medicine* marked the dawn of a new era for chemotherapy in mCRPC. DTX became the first cytotoxic agent to improve survival as well as QoL in mCRPC. One of these two studies, the TAX 327 study, compared three cohorts of 3 weekly docetaxel at 75 mg/m^2, weekly docetaxel at 30 mg/m^2 and 3 weekly mitoxantrone at 12 mg/m^2, all in combination with 5 mg prednisone twice daily (Tannock et al., 2004). The other SWOG 9916 study, compared 3 weekly docetaxel at 60 mg/m^2 plus 280 mg estramustine three times daily on days 1–5 with 3 weekly cycles of 12 mg/m^2 of mitoxantrone on day 1 plus 5 mg prednisone twice daily (Petrylak et al., 2004). In both these studies 3 weekly DTX was found to prolong the overall survival (OS) significantly compared to mitoxantrone, establishing 3 weekly DTX with prednisone(or estramustine) as the standard of care in mCRPC patients. Since then various other cytotoxic and biologic agents have been tried in combination with DTX as a first line treatment of mCRPC, but with no positive results.

Although these two trials established DTX as the standard first line treatment for mCRPC, the optimal duration of treatment is yet to be determined. The TAX trial employed DTX for 10 cycles (30 weeks) and the SWOG for 12 cycles (36 weeks). The number of cycles in these studies was so selected because the comparator mitoxantrone could result in cardiac abnormalities if used for a prolonged period (Tannock et al., 2004; Petrylak et al., 2004). In actual clinical practice, DTX is frequently continued indefinitely until unacceptable toxicity or progression of disease (PD) occurs. However, there is no clinical trial evidence to support this practice. The oncologists, therefore, are at a loss as to which approach is better-to use the drug only for 10 or 12 cycles as per the trial or to continue it indefinitely. The National Comprehensive Cancer Network (NCCN) guidelines for prostate cancer states that the duration of DTX therapy in mCRPC should be based on the assessment of benefit and toxicities pointing out to the fact that in the pivotal trials establishing survival advantage of DTX-based chemotherapy, patients received up to 10 cycles of treatment if no progression and no prohibitive toxicities were noted (Network, 2015). The Euroepan Society for Medical Oncology (ESMO) guidelines, on the other hand, has no mention of number of cycles of treatment (Horwich et al., 2013).

The overall survival benefits obtained with the use of DTX in these two trials were not highly attractive: a modest benefit of 1.9 month in the SWOG trial ($p = 0.02$) (Petrylak et al., 2004), 2.4 months ($p = 0.009$) with 3 weekly DTX but only 0.9 month ($p = 0.36$) with weekly DTX in the TAX 327 trial (Tannock et al., 2004). Furthermore, DTX is associated with a number of adverse events that can impact the QoL of mCRPC patients. Long term adverse effects of DTX include asthenia, edema, peripheral neuropathy and cytopenia (Bellmunt et al., 2007). Treatment related adverse events are an important cause of loss of QoL in elderly patients and therefore continuing chemotherapy might not be appropriate when no clear evidence of benefit exists for continuation. For low-economy regions, the extra cost associated with extra cycles of chemotherapy should also be a major consideration. The cost of DTX on top of the transport and the hospital and the doctors' fees become significant in poor economy and non-insured regions. Also, given the availability of more options of therapy post-DTX in the modern era including cabazitaxel, continuing DTX indefinitely does not seem to be as rational as it seemed a decade ago when we lacked many options.

Intermittent chemotherapy (IC) is an alternative strategy developed to address this issue. IC means allowing for a period of chemotherapy holiday (CH) when no chemotherapy agents are administered. IC can be of two types. The first is administering chemotherapy until a response is obtained after which CH is introduced which continues until for PD at which chemotherapy is resumed. The other strategy is administering chemotherapy for a certain number of predetermined cycles and allowing for a certain period of CH after which chemotherapy is resumed.

IC has been a topic of hot discussion in mCRPC treatment, because of the obvious benefits associated with IC and the absence of studies showing the inferiority of IC compared to continuous chemotherapy (CC). IC avoids prolonged exposure to DTX and therefore delays toxicity and avoids treatment-associated loss in QoL. Another benefit is IC could possibly delay the development of resistance to taxanes (Madan et al., 2011).

In a number of phase III clinical trials in breast and colorectal cancers, IC has been shown to be non-inferior in survival and possibly better in QoL compared to CC (Coates et al., 1987; Cobleigh et al., 1999; French Epirubicin Study Group, 2000; Maughan et al., 2003; Muss et al., 1991; Tormey et al., 1984). These are older trials with a few flaws in design and need careful interpretation, but they do provide an evidence for the feasibility of IC as well as the maintenance of the chemo-sensitivity of the disease upon resumption of the drug. Extrapolating these findings into prostate cancer, there have been several studies to check the validity of intermittent approach in the setting of mCRPC. Here, we introduce and summarize the trials published in English, that compared continuous with intermittent approach of DTX in the treatment of mCRPC.

3. Literature search

A comprehensive literature search was conducted with a cut-off in June 2015 of the Pubmed (MEDLINE) and relevant congresses (ASCO and ESMO) database for studies in English on metastatic prostate cancer and those studies where patients received intermittent chemotherapy either as a single arm or versus continuous therapy were included. The available studies were selected and evaluated by all the authors.

The characteristics and major outcomes of the studies that evaluated IC in mCRPC have been summarized in Tables 1 and 2.

4. Intermittent chemotherapy studies

The first study investigating the role of IC in mCRPC was done by Beer et al. even before DTX was approved as a first line therapy (Beer et al., 2003, 2004). They used criteria of reduction in prostate-specific antigen (PSA) by at least 50% (confirmed at least 4 weeks apart) and PSA nadir of <4 ng/ml for eligibility to IC but the dose of DTX used was non-standard at 36 mg/m^2 weekly. Of 37 enrolled, 30 patients showed PSA response but only 11 reached nadir PSA of <4 ng/ml. Of them, 9 chose intermittent therapy, after receiving a median of 45 weeks of chemo (range 25–53 weeks). CH lasted for a median of 20 weeks (range 13–74 weeks) and in all patients treatment was reinitiated for a rising PSA. Five patients became eligible for further CH after resumption of DTX with 50% reduc-