European Journal of Cancer xx (2018) 1–4

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Editorial

When and how to use carboplatin in metastatic castration-resistant prostate cancer?

For metastatic castration-resistant prostate cancer (mCRPC), docetaxel was the first drug to show an overall survival (OS) benefit in two large phase III trials published in 2004 [1,2]. Until 2010 when cabazitaxel and abiraterone were shown to prolong survival after first-line docetaxel chemotherapy, physicians had very little treatment options to offer for men with mCRPC, and docetaxel re-challenge was frequently used despite the lack of prospective trial data [3,4].

Platinum compounds have been tested in a large number of clinical trials either as monotherapy or in combination with various other chemotherapy agents in the setting of castration-naïve or castration-resistant disease [5]. Platinum monotherapy is associated with moderate response rates in the range of 15–20%; however, most trials were performed before the introduction of systematic guidelines on how to monitor men with advanced prostate cancer on clinical trials, which makes the interpretation of the results challenging [6–8]. Platinum compounds seem to have higher antitumour activity in combination with taxanes (docetaxel or paclitaxel) but most of the reported trials were performed in the era before docetaxel was established as standard mCRPC treatment [5]. All trials reported with platinum agents have been performed in molecularly unselected prostate cancer patients.

Advances in mCRPC molecular profiling have shown that a significant proportion of patients harbour DNA repair defects, that may confer sensitivity to platinum agents [9–12]. However, the activity of platinum in molecularly selected patients has not been prospectively tested. Two case series of prostate cancer patients with defects in DNA repair genes treated with a platinum have been published [13]. Three patients with biallelic BRCA2 inactivation had very good responses to carboplatin-based therapy, and the authors suggested that BRCA1 or BRCA2 loss could be a predictive biomarker for platinum-based chemotherapy for men with CRPC [13]. In another retrospective series of 141 men treated with a carboplatin and docetaxel combination chemotherapy, six of 8 patients (75%) with BRCA2 mutations experienced a PSA decline >50% within 12 weeks, compared with only 17% in patients without evidence of DNA repair defects (23 of 133 non-carriers) [14].

The paper presented by Bouman-Wammes *et al.* in this issue of EJC report the data of a randomised phase II clinical trial of docetaxel re-challenge compared with docetaxel in combination with carboplatin in men with mCRPC progressing at least three months after the last dose of docetaxel. This publication is important because of two aspects namely the prospective evaluation of docetaxel re-challenge and second the addition of carboplatin in a contemporaneous cohort of men with mCRPC.

The aspect of docetaxel re-challenge is interesting and the activity data (OS, PFS, PSA and objective response rate) seem considerable and also comparable with what has been published for approved and survival-prolonging second-line treatments such as abiraterone, enzalutamide, cabazitaxel and radium-223 although the interpretation is limited by the low number of patients [3,4,15,16]. It is important to note that patients included in this trial had a long median interval of almost 12 months from last dose of docetaxel to re-challenge and based on the patient characteristics, it seems that these patients have not received any other treatment before the docetaxel re-challenge. In a randomised phase II clinical trial of orteronel, switch maintenance versus placebo after a cumulative dose of $\geq$300 mg/m^2 docetaxel for first-line mCRPC treatment the median radiographic progression-free survival was 2.8 months in the placebo arm [17]. Therefore the patient

DOI of original article: https://doi.org/10.1016/j.ejca.2017.11.021.

https://doi.org/10.1016/j.ejca.2018.01.001

Please cite this article in press as: Omlin A, Gillessen S, When and how to use carboplatin in metastatic castration-resistant prostate cancer?, European Journal of Cancer (2018), https://doi.org/10.1016/j.ejca.2018.01.001

population reported in the trial by Bouman-Wammes is clearly highly selected. This may also explain the relative low rate of ≥G3 neuropathy observed with docetaxel re-challenge. Importantly, the authors did not report G1/2 toxicity especially sensory neuropathy that can be very bothersome for patients. Of note, cabazitaxel is associated with lower rates of peripheral neuropathy, alopecia, and nail disorders, which can limit the use of docetaxel re-challenge [18,19].

The second interesting aspect of this trial is the addition of carboplatin to these regimen, and the authors conclude that in unselected patients the addition of carboplatin to docetaxel did not result in improved antitumour activity. However, numerically, PSA decline rates and objective response rates were higher in the combination arm. Unfortunately the low number of patients in both arms and the premature stop of the trial make the interpretation difficult and challenge definitive conclusions. Several issues need to be taken into consideration; one of which is the dose and schedule of the combination treatment where both chemotherapy agents were not delivered at full dose (docetaxel 60 mg/m2 and carboplatin AUC4). The trial by Aparicio *et al.*[20] in *clinically* selected patients (features of aggressive variant prostate cancer) showed that both docetaxel and carboplatin can be given at full dose; however, these results were derived in the first-line mCRPC setting. Instead of selection based on clinical characteristics as done by Aparicio *et al.*[21], it is also possible to select patients based on *molecular* features such as DNA repair defects or other markers such as alterations in RB1, PTEN and Tp53 which have been shown to be correlated with sensitivity to platinum treatment.

What are the lessons learnt and where should we move on from here?

First of all, docetaxel re-challenge in clinically selected (good and long-lasting response to docetaxel) patients may be a treatment option; however the value in a more contemporaneous patient population is unclear. With the increasing use of docetaxel earlier in the disease spectrum as chemo-hormonal therapy for castration-sensitive disease where typically six cycles of docetaxel are applied the question of re-challenge with docetaxel once these men become castration resistant is more important [22,23]. Retrospective data from a small number of patients treated in the GETUG-15 trial suggest some activity of docetaxel in the CRPC setting after chemo-hormonal therapy based on PSA decline rates, notably nine cycles were given in the GETUG-15 trial [24]. The question of re-challenge will be especially interesting in countries with limited resources since docetaxel is off patent and therefore cheaper than most of the more modern options.

The biological hypothesis that men with evidence of DNA repair defects may benefit from platinum treatment similar to treatment with a PARP inhibitor needs to be tested in prospective clinical trials. Given the frequency of DNA repair defects (somatic or germline) in 15−25% of patients, the selection of patients should not be a major barrier to performing such trials [10,11,25]. Currently several clinical trials are open and enrolling namely two phase II trials of docetaxel plus carboplatin (in men with somatic or germline DNA repair defects (NCT02985021 and NCT02598895). A single arm phase II pilot study evaluates weekly carboplatin in men with mCRPC and evidence of DNA repair defects (NCT02311764). Men with evidence of DNA repair effects should be encouraged to join clinical trials. Increasingly it will also be important to test platinum agents and PARP inhibitors in sequence, especially in the light of recently presented findings of reverting germline and somatic DNA repair mutations that have been described in patients at progression on olaparib after an initial response [26].

Two trials include carboplatin in the treatment regimen in molecularly unselected men with mCRPC. A recently opened multi-arm trial includes men with mCRPC onto a combination regimen of ARN-509 plus abiraterone and prednisone, and in the other arms this combination is complemented by either ipilimumab or cabazitaxel plus carboplatin (NCT02703623). A phase I/II trial is enrolling men to sirolimus, docetaxel and carboplatin (NCT02565901).

Outside of clinical trials, the question of when to use a platinum-based chemotherapy was addressed by the last advanced prostate cancer consensus conference. In men with mCRPC who have exhausted approved treatments, and if no clinical trial was available, the majority of the panel voted for using a carboplatin-based chemotherapy for those patients; 47% of panelists would give it only to men with DNA repair defects and/or neuroendocrine differentiation on biopsy or clinical characteristics of aggressive variant, 33% would use it in the majority of patients (unselected), 2% would only use it in men with DNA repair defects and 14% only in men with neuroendocrine differentiation on biopsy or clinical characteristics thereof [27]. In men with poor prognostic, aggressive variance (excluding small-cell carcinoma), the majority of the panel (58%) voted for standard first-line mCRPC treatment but 36% voted for a platinum- and taxane-based treatment [27].

In conclusion, the increasing understanding of the molecular biology of advanced prostate cancer and the rapidly increasing availability of next-generation sequencing techniques will hopefully lead to a molecular sub-classification of prostate cancer similar to other cancer types and the presence of DNA repair defects or other molecular alterations (e.g. microsatellite instability) will predict response to systemic treatment. This progress can only be achieved through well-designed clinical trials that collect tissue and blood at serial time points for biomarker analyses. From the trial reported by Bouman-Wammes, no definitive conclusions can be drawn on the activity of carboplatin in men with mCRPC because of the lack of biomarker data and the relative small size of the trial.

Please cite this article in press as: Omlin A, Gillessen S, When and how to use carboplatin in metastatic castration-resistant prostate cancer?, European Journal of Cancer (2018), https://doi.org/10.1016/j.ejca.2018.01.001