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Chemotherapy in hormone-sensitive metastatic prostate cancer: evidences and uncertainties from the literature

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Chemotherapy in hormone-sensitive metastatic prostate cancer: evidences and uncertainties from the literature

Highlights:

- Addition of docetaxel to androgen-deprivation therapy should be the new standard of care for men newly diagnosed with metastatic prostate cancer.
- Discriminating factors to identify the best candidates to chemotherapy, like the volume of metastases, need to be validated.
- The role of docetaxel in earlier stage of the disease is under investigation.

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Abstract (220 words)

Data from the literature support with strong evidence the addition of docetaxel to androgen-deprivation therapy (ADT) for men with metastatic prostate cancer, and starting therapy for the first time. A meta-analysis of three randomized controlled trials showed a significant improvement of overall survival when ADT was combined with docetaxel when compared to ADT alone (HR=0.77; 95% CI: 0.68–0.87; $p < 0.0001$). Consequently, combination

therapy should be considered presently as the new standard of care, using 6 cycles of docetaxel, without prednisone.

However, candidates for this upfront combination therapy in whom the balance between its side effects and benefits is favorable are still to be identified more precisely. Patients' stratification according to Gleason score, previous local treatment and age or performance status were shown to have a prognostic impact. The volume of metastases, as defined in the CHAARTED study for instance, could be an interesting predictive factor. However, data accumulated until now remain only hypothesis generating and further analysis and studies are needed to establish any potential discriminating factors.

Several new efficient therapeutic options are now available in prostate cancer management and should be evaluated against a chemo-hormonal combination therapy. Other trials are warranted to establish the role of docetaxel in earlier stages of the disease, the combination with the new hormonal therapies as well as the best management options after docetaxel.

Introduction

Prostate cancer (PCa) has the highest incidence of all solid tumors in Europe, which is estimated to be >200 cases per 100,000 men [1]. It is a major health problem concern, especially in developed countries with a greater proportion of elderly men in the general population. Metastatic prostate cancers at diagnosis occur in less than 10% of patients in developed countries [2]. In less developed countries, metastatic disease is the most common presentation of PCa, which represents an important public health issue. In recent years, the median survival of patients with newly diagnosed metastases was 42 months [3].

Over 70 years ago, Huggins and Hodges as well as Niehans demonstrated the responsiveness of symptomatic metastatic PCa to castration. Androgen deprivation therapy (ADT) is the current standard of care in first-line metastatic setting [4]. Before new active drugs were introduced, median survival with ADT varied from 31 to 49 months [5]. However, the outcome of this treatment varies widely and resistance to ADT occurs in most patients. Median duration of sensitivity to ADT is usually 24–36 months [6]. In patients with resistance to ADT, docetaxel plus prednisone therapy resulted in a median survival that was approximately 2.5 months longer than that with mitoxantrone and prednisone [7]. Three randomized controlled trials were conducted at an earlier stage, in patients with hormone-sensitive metastatic PCa, comparing ADT alone as a standard to an experimental arm combining ADT with upfront docetaxel [8]. These trials reported findings regarding survival benefits that are not all statistically significant. In order to discuss these results, 16 French specialists in onco-urology, including urologists, radiation therapists and medical oncologists, worked together. The aim of this work was to present the evidence from the literature and the remaining questions regarding the benefit of early chemotherapy in patients with hormone-sensitive metastatic PCa. This article is summarizing their work.

Results from the published trials comparing ADT alone to ADT plus docetaxel in hormone-sensitive metastatic PCa

Three randomized controlled trials were conducted in patients with hormone-sensitive metastatic PCa, comparing ADT alone as a standard to an experimental arm combining ADT with upfront docetaxel. For these 3 trials, there was no blinding to treatment allocation and the primary endpoint was overall survival.

GETUG-AFU 15 trial (NCT00104715)

In this French randomized, open-label, phase 3 trial, 192 patients with metastatic PCa were randomly allocated to receive ADT plus docetaxel (75 mg/m² intravenously on the first day of each 21-day cycle; up to 10 cycles, like in the TAX 327 study) without daily prednisone and 193 to receive ADT alone [8]. The trial started in 2004, at the beginning of docetaxel use in daily practice. Median follow-up was 50 months (IQR 39–63). Median overall survival (OS) was 58.9 months (95% CI: 50.8–69.1) in the ADT plus docetaxel group and 54.2 months (42.2–not reached) in the ADT alone group (HR=1.01, 95% CI: 0.75–1.36) meaning that the primary endpoint of this trial was not met.

The initial risk stratification of the patients was performed according to the Glass classification [9], including tumor volume, Karnofsky index, Gleason score and PSA, defining 3 risk-groups of patients. After the publication of the CHAARTED trial, the data on metastatic volume from medical files of all patients included in the GETUG-AFU 15 trial were retrospectively retrieved, applying the CHAARTED definition of low and high volume disease and updated survival analysis [10]. Patients included in GETUG-AFU 15 had a low volume disease in more than 50% of cases. After a median follow-up of 83.9 months, median OS in the overall population was 62.1 months (95% CI: 49.5–73.7) and 48.6 months (95% CI: 40.9–60.6) for ADT plus docetaxel and ADT arms, respectively (HR=0.88; 95% CI: 0.68–1.14; p=0.3). For high-volume disease patients, median OS in ADT plus docetaxel was: 39.8 months (95% CI: 28.0–53.4) versus 35.1 months (95% CI: 29.9–43.6) (HR=0.78; 95% CI: 0.56–1.09; p=0.14) in the ADT arms, respectively. For low-volume disease patients, median OS was not reached (NR; 95% CI: 69.5–NR) in the combination arm and was 83.4 months (95% CI: 61.8–NR) (HR=1.02; 95% CI: 0.67–1.55; p=0.9) in the ADT arm. For upfront metastatic patients, OS was 52.6 months (95% CI: 43.3–66.8) and 41.5 months (95% CI: 36.3–54.5), respectively (HR=0.93; 95% CI: 0.69–1.25; p=0.6). In this post-hoc analysis of the GETUG-AFU15 trial, a

non-significant 20% reduction in the risk of death in the high-volume disease subgroup was found, but patients with low-volume disease had no survival improvement with early docetaxel.

CHAARTED trial (NCT00309985)

The design of this trial was substantially the same as GETUG-AFU 15, but the patients were supposed to receive 6 cycles of docetaxel (without daily prednisone) instead of 10 [11]. The study was initially designed for patients with high-risk disease, defined as PCa with visceral metastases or more than 3 bone metastases with at least 1 appendicular localization. Secondly, patients with low-volume disease were also included, due to difficulties for recruitment. As a consequence, patients with low-volume had a shorter follow-up. A total of 790 metastatic patients (median age, 63 years) underwent randomization. Prior adjuvant ADT was allowed if the duration of therapy was 24 months or less and progression had occurred more than 12 months after completion of therapy. After a median follow-up of 28.9 months, the median OS was 13.6 months longer with the combination therapy than with ADT alone (57.6 months vs. 44.0 months; HR=0.61; 95% CI: 0.47-0.80; $p<0.001$). When stratifying according to the volume of the disease, the benefit at the last analysis was more apparent in the subgroup with high-volume disease (HR=0.60; 95% CI: 0.45-0.81; $p<0.001$) than in patients with low-volume disease. However, the median survival for low-volume disease patients has not been reached at the time of the analysis (HR=0.60; 95% CI: 0.32-1.13; $p=0.11$).

STAMPEDE trial (NCT00268476)

STAMPEDE is a randomized controlled trial using a multiarm, multistage platform design [12]. It started in 2005, recruiting men with high-risk, locally advanced, metastatic or

recurrent PCa who started first-line long-term hormone therapy. Standard of care was hormone therapy for at least 2 years. Stratified randomization allocated men 2:1:1:1 to standard of care only (SOC-only; control), standard of care plus zoledronic acid (SOC+ZA), standard of care plus docetaxel (SOC+Doc), or standard of care with both zoledronic acid and docetaxel (SOC+ZA+Doc). Docetaxel (75 mg/m²) was given for six 3-weekly cycles with daily prednisolone 10 mg daily. Overall, 2962 men were randomly assigned to four groups between October 2005, and March 2013. 165 (6%) men were previously treated with local therapy. After a median follow-up of 43 months (IQR 30–60), median OS was 71 months (IQR 32 to not reached) for SOC-only and 81 months (41 to not reached) for SOC+Doc (HR=0.78, 95% CI: 0.66–0.93; p=0.006). For patients with metastatic disease, the HR for SOC+Doc was 0.80 (95% CI: 0.65-0.99; p=0.033). Zoledronic acid showed no evidence of survival improvement.

Meta-analysis and discrepancies between reported trials

A meta-analysis of these three trials was performed and confirmed the overall survival improvement by adding upfront docetaxel to ADT in hormone-sensitive metastatic PCa [13]. Assuming a typical 4-year survival with standard of care of 40%, the meta-analysis HR of 0.77 (95% CI: 0.68-0.87; p<0.0001), translates to a 9% (95% CI: 5-14) absolute improvement with standard of care plus docetaxel compared to standard of care alone.

However, there are some discrepancies between the populations included in the 3 trials (Table 1). The period of inclusion varies for GETUG-AFU 15 from 2004 (year of the approval of docetaxel in daily practice) to 2008, 2006-2012 for CHAARTED and 2005-2013 for STAMPEDE. There were less patients included in GETUG-AFU 15 (N=385) compared to the other trials. Regarding the ECOG performance status, 98% of the patients included in GETUG-AFU 15 were ECOG 0, versus only 69% in CHAARTED and 72% in the control group of

STAMPEDE. The proportion of patients with metastases at the time of diagnosis was the same in GETUG-AFU 15 and CHARTED but the proportion of high-volume disease was more important in CHARTED. There was no information on the volume of metastases in the STAMPEDE trial. The Gleason score was higher in CHARTED and STAMPEDE. The median number of cycles of administered docetaxel was more important in GETUG-AFU 15 (9 cycles) than in the two other studies (6 cycles). Four treatment-related deaths occurred in the ADT plus docetaxel group in the GETUG-AFU 15 trial (two of which were neutropenia-related). There was only one death due to treatment toxicity in CHARTED and eight in STAMPEDE (one on SOC+Doc and seven on SOC+ZA+Doc including four neutropenic sepsis). The median follow-up was higher in GETUG-AFU 15 (83 months) versus 29 months in CHARTED and 43 months in STAMPEDE. For the 3 trials, biochemical and radiological progression-free survival were significantly improved in the ADT plus Docetaxel arm, which raises the question of treatments administered beyond progression: 85% of the patients in GETUG-AFU 15 received docetaxel, versus 48% in CHARTED and 41% in STAMPEDE. As a consequence, although data from the literature provides substantial and reliable evidence that adding docetaxel to standard of care improves the survival of men with hormone-sensitive metastatic disease, several questions remain before this treatment is offered to all men who are fit to receive chemotherapy.

Role of docetaxel in patients with low-volume disease

No predictive factors are currently available to identify which patient will benefit from the upfront chemotherapy-ADT combination. However, volume of metastases could possibly be a relevant predictive factor. The definition of high-volume disease used in the CHARTED trial was a combination of features from prior classifications. All the definitions included the presence of visceral disease as a predictor of poor prognosis. According to the definition of the South-West Oncology Group, any lesion beyond the vertebrae and pelvis, irrespective of

total lesion count, would be classified as “extensive” [14]. In the CHAARTED trial, the site of bone metastases combined with the number of metastases was considered to avoid classifying patients with four or fewer metastases as having high-volume disease, even if one lesion was beyond the vertebrae and pelvis.

In the subgroup of patients with high-volume disease, the median OS was 17 months longer in the combination group than in the ADT-alone group (49.2 months vs. 32.2 months). In contrast, median OS was not significantly different (HR=0.60; 95% CI: 0.32-1.13; p=0.11) in patients with low-volume disease. However, the median survival had not been reached at the time of the analysis. Furthermore, the inclusion of patients with low-volume disease was only allowed at a late stage of the inclusion (in order to speed up recruitment) and thus the follow-up of these patients was much shorter than for the high volume subgroup.

In the STAMPEDE trial, the survival benefit is clear in metastatic subpopulation, which accounted for 61% of patients in the trial. But the volume of metastases was not considered as a criterion for subgroup analysis.

In the post-hoc analysis of GETUG-AFU 15, patients with high-volume disease had a median OS improvement of 4.7 months in the ADT plus Docetaxel arm, but the difference was not statistically significant as compared to the ADT arm: 39.8 months (95% CI: 28.0–53.4) versus 35.1 months (95% CI: 29.9–43.6) (HR=0.78; 95% CI: 0.56–1.09; p=0.14) (Table 2). The lack of significant OS benefit with ADT plus docetaxel in patients with high volume disease in GETUG-AFU15, despite a significant improvement in biochemical and radiological progression-free survival may thus have resulted of 2 combined phenomenon: a much lower median OS with ADT plus docetaxel as compared to CHAARTED (39.8 months versus 49.2 months) and a slightly better median OS in the ADT arm (35.1 months versus 32.2 months). Since both studies had a similar design, several hypotheses have been proposed to explain these discrepancies. First, the CHAARTED study included twice as many patients as the

GETUG-AFU 15 study, leading to possible insufficient power for the GETUG-AFU15 trial to demonstrate a benefit of chemotherapy. Second, patients in the CHARTED trial had worse prognosis and, were perhaps more likely to gain benefits from chemotherapy: 64% and 66% had high volume disease in the ADT and ADT plus Docetaxel arms, respectively, versus 47% and 48%, respectively, in the GETUG-AFU 15. Eastern Cooperative Oncology Group (ECOG) performance status was 1–2 in 30.5% of patients versus 2.3% in the GETUG-AFU15 trial; high Gleason score (8–10) was found in 61% of patients versus 57%, and median PSA was approximately twice higher. These differences can partly explain the higher OS in the ADT control group (medians: 54.2 vs 44.0 months). Third, in the subgroup of patients with high volume disease, the much lower median OS with docetaxel plus ADT as compared to CHARTED (39.8 vs 49.2 months) and slightly better performance of the ADT arm (35.1 vs 32.2 months) raises the question of life-extending treatments administered beyond progression. In the CHARTED trial, besides Docetaxel that some patients received beyond progression (48% of patients with progressive disease in the ADT arm and 22.7% in the ADT plus Docetaxel arm), those in the ADT plus Docetaxel arm received numerically more frequently drugs that were previously shown to improve OS than patients in the ADT alone arm: cabazitaxel (23.9% and 12.9%), abiraterone and/or enzalutamide (44.1% and 36.2%), and sipuleucel-T (9.2% and 6.6%) (Table 3). Taken together, this indicates that patients in the experimental arm received life-extending drugs more frequently, either at randomization (Docetaxel) or beyond progression, than patients in the control arm. In the GETUG-AFU15 study, the vast majority of patients (85%) in the ADT arm received so-called salvage Docetaxel within a median time of 18.5 months (95% CI, 2.9–179) while only 48% of patients received salvage docetaxel in CHARTED trial. The percentage of patients receiving other life-extending treatments (abiraterone, enzalutamide, and cabazitaxel) beyond progression in ADT arm was rather similar between GETUG-AFU 15 and CHARTED. The much higher use

of salvage docetaxel in the ADT arm of GETUG-AFU 15 (85%) as compared to CHARTED (48%) and STAMPEDE (41%) may contribute to explain the better performance of GETUG-AFU 15 ADT arm (Table 2) [15].

Gleason score and chemotherapy benefit

Subgroup analysis using prognostic factors like Gleason score, showed that there was a benefit of ADT + Docetaxel versus ADT whatever the Gleason score. Surprisingly, it seems that the benefit of docetaxel in survival is more important for patients with Gleason score \leq 7. These results are remarkable in CHARTED and there is a trend in both GETUG-AFU 15 and STAMPEDE, even if there is a lack of specific data for the metastatic patients in these last trials. This trend was also found in earlier stage in the GETU-AFU 12 study [16]. The explanation for this effect remains unknown. However, it seems important to have a centralized histologic analyze with dedicated uro-pathologist to prevent mis-interpretation.

Influence of local treatment

In all three randomized trials, most of the men who were randomly assigned to treatment groups were newly diagnosed with metastatic disease, but patients initially treated for local disease could also be included. In the GETU-AFU 15 trial, these patients represented 28% of cases, and had a significantly longer survival (83.1 vs 46.5 months; HR=1.57; 95% CI: 1.09–2.26; p=0.015). But no significant difference in OS was observed between treatment arms (ADT plus Docetaxel vs ADT) between patients with de novo and secondary metastatic diseases. In the CHARTED study, 27% had previous local treatment and there was no benefit to docetaxel in this subgroup population (HR=0.55; 95% IC: 0.23-1.31; p>0.05). These

patients usually have a good follow-up and the metastatic progression is more commonly diagnosed at an earlier stage. For this population, the benefit of Docetaxel and ADT combination is less obvious.

Association of prednisone with docetaxel

In the three trials of docetaxel in hormone-sensitive metastatic PCa, prednisone was not co-administrated with docetaxel except in the STAMPEDE study (prednisone 10mg/day).

In patients with androgen deprivation therapy, it is supposed that low dose of prednisone could influence fatigue, nausea and the number of circulating granulocytes. Furthermore, multiple studies have confirmed an effect on PSA levels [17]. In a recent retrospective study of 358 patients, co-administration of low-dose prednisone reduced the incidence of peripheral edema, grade 3 non-hematologic toxicity and the risk of being admitted owing to febrile neutropenia during treatment with docetaxel [18]. Adjusted survival analysis did not indicate the prednisone affected prognosis. However, the patients included had metastatic castration-resistant PCa.

Furthermore, prednisone can affect the clearance of docetaxel, it can hide the manifestations of febrile neutropenia and it has long-term effects on osteoporosis. There was no obvious benefit in terms of febrile neutropenia (12% in STAMPEDE versus 6-8% in GETUG-AFU 15 and CHAARTED) in the three trials. As a consequence, prednisone doesn't seem to be useful in association with docetaxel in hormone-sensitive setting.

What is the optimal number of cycles of docetaxel in hormone-sensitive metastatic PCa?

It seems that the standard in hormone-sensitive metastatic PCa is 6 cycles of docetaxel. This was the design of the randomized trials, except for GETUG-AFU 15 with 10 cycles initially planned and a median of 9 cycles administrated.

Adverse effects of chemotherapy and patients' self-assessment

Across the three trials, the number of reported grade 3–4 adverse events increased with docetaxel, most commonly neutropenia. In the meta-analysis of Vale et al., 16 deaths were attributed to docetaxel, including 4 in the GETUG-AFU 15, in the early experience of docetaxel use. Data from the GETUG-AFU 15 study showed that adverse events after docetaxel treatment should be closely monitored, and the frequency of severe neutropenia should be limited by granulocyte colony-stimulating factor. Before the amendment of the study protocol to allow administration of granulocyte colony-stimulating factor, grade 3–5 neutropenia was noted in almost a third of patients, 7% of patients had febrile neutropenia, and two patients died from neutropenia-related conditions. However, after the amendment, the frequency of neutropenia and febrile neutropenia of grade 3–4 decreased substantially and no subsequent toxic deaths occurred.

In the CHARTED trial, approximately 6% of the patients in the combination group had neutropenic fever, and approximately 2% had grade 3 or 4 infection with neutropenia. In the STAMPEDE study, febrile neutropenia occurred in up to 15% in the arm SOC + Docetaxel. Febrile neutropenia after docetaxel treatment was more frequent in these studies than in previous.

One explanation could be that docetaxel clearance is increased by about 100% in men with castration-resistant PCa compared with those with non-castrate disease, and is associated with a two-fold reduction in the area under the curve, although hepatic activity of cytochrome P450 3A4 is unchanged ($p=0.0001$), probably because of an increase in hepatocyte uptake [19]. This is concordant with the results of TAX 327 with 3% of febrile neutropenia in patients with castration resistant metastatic PCa [7].

However, physicians should keep in mind that they often fail to report symptoms of cancer treatment toxicity, even the most common and disturbing ones [20]. Patients are the best source of information about their own symptoms and a self-assessment of toxicity would improve patient's care and consequently medical outcome. Consequently, the continuation of chemotherapy should be carefully evaluated.

Data about patient's quality of life were only published in the GETUG-AFU 15 trial: quality of life was altered during chemotherapy, but it improved rapidly at the end of the treatment, except for constipation. The quality of life should be taken into account, and the balance between duration of toxicity and survival without progression seems to be in favor of chemotherapy in high-volume disease. QoL analysis of the phase III CHARTED study was presented at the 2016 ASCO meeting. Patients receiving ADT+D reported a lower QOL at 3 months but a significantly better QOL at 12 months compared with patients receiving ADT alone, suggesting longer preservation of QOL for patients receiving ADT+D in addition to survival benefits (Miller L et al. Abstract 5004).

Docetaxel in elderly patients

Age is often considered a limitation to the administration of docetaxel. The oncogeriatric evaluation of the patient is of high importance, and practical tools like the onco-G8 score are now available to detect patients who would benefit from comprehensive geriatric assessment [21].

In a subgroup analysis of the TAX327 study, the survival improvement with 3-weekly docetaxel compared with mitoxantrone was similar for patients aged 68 years or younger and those older than 68 years (hazard ratios 0.81 vs 0.77, not significantly different) [22].

In a retrospective analysis of patients aged 75 years or older treated with docetaxel (either 3-weekly or weekly regimen according to clinical judgment), patients with a good performance status showed responses similar to those of younger patients, and it was generally well tolerated [23]. In both CHARTED and STAMPEDE, there was a benefit for docetaxel whatever the age. However, in most studies, patients are highly selected which can differ from real life practice [24].

Surveillance and early detection of progression

The surveillance of the patients under treatment is an important issue that can influence the outcome. Close radiological and biological monitoring could result in increasing the number of treatment lines, which might be associated with better overall survival [25]. Clinical indications for the use of imaging in PCa depend on the different phase of the disease. Magnetic resonance imaging (MRI) and positron emission tomography (PET) with radiopharmaceutical agents showing a tropism for PCa cells have been introduced into clinical guidelines. In restaging, the detection rate of $^{11}\text{C}/^{18}\text{F}$ -choline PET/CT is $> 80\%$ if PSA level $> 2\text{ng/mL}$, but it falls $< 20\%$ if PSA level $< 1\text{ng/mL}$, and it lacks micro-metastatic ($< 2\text{mm}$) lymph node and liver metastases [26]. Few papers have discussed the role of radiolabeled choline PET/CT for the assessment of the response to chemotherapy. Recently, Ceci et al. have demonstrated the utility ^{11}C -choline PET/CT to assess the response to docetaxel in 61 patients with metastatic PCa, with a greater role for progressive disease [27]. These results are preliminary and future prospective studies are needed to assess the role of radiolabeled PET/CT as a tool for early response assessment to chemotherapy. Alternative PET tracers, like PSMA, are promising, although there are not yet available in many countries [28]. A close follow-up of the patients under treatment is important to early detect the non-responding-patients but also to prevent side effects and medical interactions in this

population of patients with frequent comorbidities. Currently no data are available on how patients should be followed after ADT-docetaxel exposure for hormone-sensitive metastatic PCa.

Post-docetaxel treatments and cross-resistance

There is currently no evidence in the literature to define the best treatment option after progression after first line of docetaxel + ADT. Several criteria may influence the choice of the second line of treatment: interval between the end of treatment and progression, symptomatology and quality of life of the patient as well as toxicity experience of the previous treatment. In the literature, new hormone therapies (abiraterone, enzalutamide) [29] and chemotherapy (cabazitaxel) [30] have proven an overall survival benefit in metastatic castration-resistant PCa progressing after docetaxel. But there is no data available in the setting of progression after chemotherapy in hormone-sensitive metastatic PCa.

Data from basic research support the development of cancer as an ongoing Darwinian evolutionary process, leading to multiple competing subclones within the primary tumor but also in the metastases [31]. Recently, polyclonal seeding and interclonal cooperation among different metastases in the context of androgen deprived metastatic PCa has been reported [32]. Metastasis to metastasis spread was found to be common, either through de novo monoclonal seeding of daughter metastases or through the transfer of multiple tumor clones between metastatic sites.

The current strategy in metastatic PCa is sequential: after failing to respond optimally to one drug, the patient is switched to another. This approach may increase the risk of multidrug resistance by selecting subpopulations of tumor cells within the tumor that have multiple mechanisms of resistance, conferring resistance to all therapies. No single drug can prevent

all forms of resistance. Extrapolating from the experience with other diseases, a combination of two or more therapies with non-overlapping mechanisms of resistance may prevent the emergence of drug resistance. More intensive upfront therapy, with the goal of killing all PCa cells, should help to stop drug resistance developing. Data from STAMPEDE and CHARTED validate this hypothesis. The PEACE-1 trial is currently recruiting patients to compare in a randomized phase 3 study the clinical benefit of androgen deprivation therapy with or without local radiotherapy with or without abiraterone acetate and prednisone in metastatic hormone-naïve PCa. A recent amendment allows administering docetaxel to all patients. This will be a good opportunity to evaluate its association to the new hormonotherapies, with or without local treatment.

Conclusion

Data from the literature provide substantial and reliable evidence on the benefit of adding docetaxel to ADT in hormone-sensitive metastatic PCa. However, there are still no predictive factors to identify the best candidates and optimum time for chemotherapy. The level of evidence to support a benefit of docetaxel in high-volume disease is high. Since PCa is a very early heterogeneous disease, it is hypothesized that chemotherapy plus ADT would work in both situations. Consequently, there is an urgent need to identify clinical and/or molecular predictive factor in order to help physician to take the best treatment decision. Other trials will provide information on the use of docetaxel in even earlier stages of the disease, and also on the best options after docetaxel exposure. The paradigm shift lies in the fact that physicians have to deal with several effective therapeutic options for metastatic PCa. The combination of these treatments, including new hormonotherapies, might be the next step forward.

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Tables

Table 1: Characteristics of the patients in the three randomized controlled trials

Table 2: Outcome of the patients in the three randomized controlled trials

Table 3: Subsequent life extending therapies in the three randomized trials

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Table 1: Characteristics of the patients in the three randomized controlled trials

	GETUG-15 [7]	CHAARTED [10]	STAMPEDE [11]
Period of inclusion	10/2004 - 12/2008	07/2006 - 11/2012	10/2005 - 03/2013
N	385	790	2962
ECOG PS:			
0	98% (357)	69.5% (549)	72% (662) ADT arm*
1-2	2% (9)	30.5% (241)	28% (225) ADT arm*
Local treatment before metastatic progression	28% (108)	27% (214)	NA
Metastatic at diagnosis	72% (272)	72.8% (575)	61% (1817)
Burden of metastases:			
High volume disease	48% (183)	65% (513)	NA
Low volume disease	52% (202)	35% (277)	
Gleason score \geq 8	56% (216)	61.2% (484)	64% (587) ADT arm*
Number of cycles of Docetaxel	9	6	6 + prednisone 10mg/d
Treatment related death	4	1	8
Docetaxel after progression in ADT arm	85%	48%	40%
Median follow-up (months)	83	29	43

PS: performance status

*James Eur Urol 2015

Table 2: Outcome of the patients in the three randomized controlled trials

	GETUG-15 [7]	CHAARTED [10]	STAMPEDE [11]
Median OS ADT/ADT + D	48.6/62.1 HR 0.9 (0.7-1.1)	44/57.6 HR 0.61 (0.47-0.80)	45/60 HR 0.76 (0.62–0.92)
Median OS HVD ADT/ADT + D	35.1/39.8 HR 0.8 (0.6-1.1)	32.2/49.2 HR 0.6 (0.45-0.81)	NA
Median OS LVD ADT/ADT + D	83.4/NR HR 1.0 (0.7-1.6)	NR/NR HR 0.6 (0.32-1.13)	NA
Median PFS ADT/ADT + D	12.9/22.9 HR 0.7 (0.6-0.9)	11.7/20.2 HR 0.61 (0.51-0.72)	M1: HR 0.61 (0.53-0.71)

OS: overall survival; ADT: androgen deprivation therapy; D: docetaxel; HVD: high volume disease; LVD: low volume disease

Table 3: Subsequent life extending therapies in the three randomized trials

	GETUG15 [10]		CHAARTED [7]		STAMPEDE [11]	
	ADT + DOC N=192	ADT alone N=193	ADT + DOC N=397	ADT alone N=393	ADT + DOC N=592	ADT alone N=1184
N pts with progression		N=149	N=238	N=287	N=315	N=761
Docetaxel	N=54	N=127 (85%)	22.7%	48%	14%	41%
Cabazitaxel	N=16	N=15 (10.1%)	23.9%	12.9%	7%	3%
Abiraterone/ enzalutamide	N=48	N=48 (32.2%)	44.1%	36.2%	36.2%	31.9%
Sipuleucel-T	0	0	9.2%	6.6%	0	0
Radium 223	0	0	0	0	2%	1%

Highlights

- Addition of docetaxel to androgen-deprivation therapy should be the new standard of care for men newly diagnosed with metastatic prostate cancer.
- Discriminating factors to identify the best candidates to chemotherapy, like the volume of metastases, need to be validated.
- The role of docetaxel in earlier stage of the disease is under investigation.

ACCEPTED MANUSCRIPT