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The Hormonal Strategy in Castration-Sensitive Metastatic Prostate Cancer: Should it be Redefined in 2018?

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Abstract

Introduction: Management of metastatic prostate cancer castration sensitive has undergone a remarkable change. Several drugs have demonstrated benefits in castration resistance. Recently, their use in the novo metastatic patients has proved to be effective in overall survival. This review focuses on therapeutic news and its impact on clinical practice for the patient and the oncologist.

Materials and methods: The Medline database was accessed using the following keywords: neoplasm prostate, metastatic, Androgen deprivation therapy, Docetaxel, Abiraterone, Enzalutamide, bisphosphonates. We reviewed data from randomized studies published or presented at international conferences until 2018.

Results: Androgenic deprivation in all these galenic forms remains the backbone of the treatment. Compared to androgen deprivation alone, the addition of Docetaxel or abiraterone acetate improves overall survival in defined high-risk patients. Both approaches were not compared directly. Castration alone remains to be discussed in other patients.

Conclusion: Castration sensitive metastatic prostate cancer (CSMPC) is a heterogeneous disease. The Androgenic suppression is still the backbone of treatment, the addition of Docetaxel or Abiraterone acetate has improved outcomes and become standard of care. Treatment of patients with (CSMPC) requires a multidisciplinary approach. Patient comorbidities and characteristics of prostate cancer should guide our therapeutic choice.

Keywords: Metastatic prostate cancer; Castration sensitive; Androgen suppression; Docetaxel; Abiraterone

Introduction

Prostate cancer is highly heterogeneous with 26% of samples driven by unknown molecular alterations; 7 subtypes defined by ETS transcription factor gene fusions or mutations in *SPOP*, *FOXA1*, or *IDH1*; actionable lesions in the PI3K, MAPK, and DNA repair pathways [1]. Androgen-Deprivation remains the mainstay of castration-sensitive prostate cancer therapy. The benefit is noticed in terms of progression-free survival without impact on overall survival. The duration of disease control varies from 18 to 36 months with better control of symptoms [2-9]. The understanding of the molecular mechanisms of resistance to castration has allowed the development of several molecules. A second line has become possible with improved survival using either cytotoxic chemotherapy or next-generation hormone therapy [3-7]. The use of these molecules in hormone-naive patients has demonstrated a remarkable benefit in overall survival. The choice of the molecule to add to the androgen deprivation has become complicated. Considering different data from the literature, the aim of this review is to review whether the treatment of prostate cancer from the outset metastatic hormone-sensitive must be redefined in 2018.

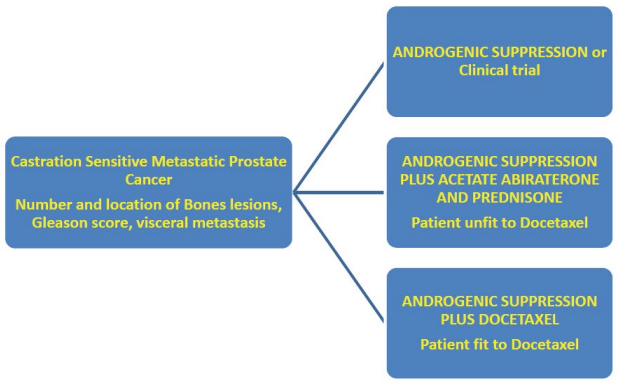

Figure 1: Hormonal strategy for castration sensitive metastatic prostate cancer patients.

Literature Review

The medline database was searched using the following keywords: neoplasm prostate, metastatic, Androgen deprivation therapy, Docetaxel, Abiraterone, Enzalutamide bisphosphonates. This review was carried out based on data from recommendations in onco-urology (French Association Urology, European Association of Urology, and European Society of Medical Oncology) and randomized studies

Phases	Chaarted	Stampede Docetaxel	Getug 15	Latitude	Stampede Abiraterone
Follow-up Median	28,9	43	50	30,4	40
Median overall survival	57.6 *vs.* 44 (0.61)	81 *vs.* 71 (0.78)	58.9 *vs.* 54.2 (1,01)	NR *vs.* 34.7	ND
overall survival at 3 years	70 *vs.* 55 ~ 77	~77 *vs.* 73	64.2 *vs.* 62.9	66 *vs.* 49 (0,62)	83 *vs.* 76 (0,63)
Median of progression-free survival (month)	ND	37 *vs.* 20	ND	33 *vs.* 14.8	43.9 *vs.* 30
3y FFS (%)	ND	~52 *vs.* 39	ND	ND	75 *vs.* 45

Table 1: Phase III studies in castration-sensitive prostate cancer.

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Allergic reaction to Docetaxel	
Disrupted liver status	(ASAT and ALT>5 times normal and or bilirubin> 3 times normal)
Neuropathy	>Grade 2
Platelet rate	<50,000 and neutrophil rate <1000 / mm^3
Performance status	>2
Fragile elderly G8	<14

Table 2: Patients unfit to Docetaxel.

published or presented at international conferences having an impact on the treatment patients until 2018.

Results and Discussion

Androgenic suppression alone

The treatment of hormone-sensitive metastatic prostate cancer is based on Androgenic suppression. Several galenic forms have shown their effectiveness. Bilateral orchidectomy allows a rapid reduction of testosterone, simple, inexpensive but irreversible achievement with a negative psychological effect for patients [2-9]. Medical castration by agonist or antagonists Gonadotropin-releasing hormone agonists (GnRH) results in a similar therapeutic effect without psychological impact for patients, reversible but expensive, especially since it is a treatment for life and currently the question of price has begun to take an important place in the health economy [10]. The Seidenfeld Meta-analysis published in 2000, covering 24 trials and more than 6,600 patients with locally advanced or metastatic cancers, shows that GnRH agonists alone are the standard treatment [8]. The addition of conventional anti-androgens to medical castration to complete the androgen blockade shows an improvement in survival of 2% not significant at the cost of an impairment of quality of life [9]. For patients managed with medical orchidectomy, antiandrogen is indicated for two to four weeks during GnRH agonist initiation to prevent a disease flare due to the transient increase in testosterone levels. The use of the antagonists is not inferior to the agonists but a difficult tolerance with more pain at the injection site [11]. Early castration allows a reduction in specific mortality (relative risk [RR] 0.84, 95% CI 0.77-0.92), risk of progression and cancer-related symptoms [12]. In order to delay the onset of resistance and improve the quality of life, the SWOG 9346 study did not conclude that the intermittent versus continuous regimen was not inferior [13]. The use of anti-androgens alone is not recommended [14].

Androgenic suppression combined with another molecule (Docetaxel and abiraterone)

Several reasons pushed the investigators to think about new therapeutic strategies among which, limited effectiveness of medical castration alone, a different prognosis depending on whether it is a "minimal" disease (axial involvement [rachis, pelvis] or nodes) or "extensive" disease (appendix involvement, long bones, ribs, skull or visceral involvement). With continuous hormone therapy, for patients with PSA <4 ng/ml after 6 months of castration, median survival is 6.9 years in "minimal" disease vs. 4.4 in "extensive" disease. However, patients who have a PSA >4 ng/ml after 3 months of treatment have a median survival of 16 months versus 69 months if the PSA is <4 ng/ml [15,16]. Similarly, patients who have a PSA increase of more than 25% on hormone therapy have a poorer prognosis with a median survival of 10 months versus 44 months, the availability of effective molecules in castration resistance with an improvement of overall survival demonstrated in several large and relatively well-supported Phase III studies in a well-selected patient population [3-7]. Rational of Chemo-Hormonotherapy is to eradicate hormone-resistant clones of prostate cancer. For these metastatic setting, with criteria of poor prognosis, two new therapeutic approaches could be considered. The medical castration combined with Docetaxel was evaluated in three phase III studies (CHARTEED, STAMPEDE and GETUG15). These studies were compiled in a meta-analysis. A total of 2 262 patients (951 under Docetaxel and ADT, 1 311 ADT alone) with metastatic disease were reviewed. The addition of Docetaxel was associated with an improvement in OS (RR=0.73, 95% CI 0.60-0.90, p=0.002) with non-significant heterogeneity between trials and improvement. Progression-free survival in patients with metastases (RR=0.63, 95% CI: 0.57-0.70, p<0.001) [17-20]. The patients received 6 cycles in total without associated corticosteroids. This combination was responsible for myelosuppression with grade 3 and 4 neutropenia incidence between 6 and 15% with 8 toxic deaths noted in the STAMPEDE study [18]. Abiraterone acetate has been shown to be effective in pre- and post-chemotherapy castration-resistant disease, in castration-sensitive metastatic prostate patients with high risk factors (with 2 of the 3 prognostic criteria: Gleason score >7, at least 3 bone lesions and at least one measurable visceral lesion), abiraterone was evaluated in the LATITUDE study [21]. A total of 1199 patients were randomized androgen deprivation plus abiraterone acetate (1000 mg once daily) and prednisone (5 mg daily) to androgen deprivation plus placebo. With a median follow-up of 30.4 months, the combination of abiraterone acetate with androgen deprivation demonstrates a significant overall survival advantage over placebo: median survival not achieved vs. 34.7 months (random ratio, 0.62, 95% confidence interval [95% CI], 0.51 to 0.76, p<0.001). These results were confirmed in a second STAMPEDE study that reported the same magnitude of benefit [22]. In terms of tolerance, known side effects have been reported more frequently with abiraterone-prednisone acetate such as hypertension and hypokalemia (grade 3 and 4 hypertension: 20% and 10% vs. 0% and 0, 2%, grade 3 and 4 hypokalemia: 10% and 0.8% versus 1% and 0.2%). Several trials with Enzalutamide in this situation are in progress but no results are available.

Castration-sensitive metastatic prostate cancer and management of Bone metastases

In castration-resistant prostate cancer Zoledronic acid decreases the risk of occurrence of skeletal-related events. Its early use in castration-sensitive metastatic prostate cancer was evaluated in two Phase III studies. STAMPEDE trial randomized evolutionary design (multi arm and multi stage) intended to answer several questions among which, the place of Zoledronic acid in a Hormono-sensitive situation with chemo-castration 2962 patients with prostate cancer with bone metastases were randomized to 4 arms (SA +/- Zoledronic acid and SA+Docetaxel +/- Zoledronic acid). A decrease in the risk of occurrence of the first symptomatic bone event of 40% in patients treated with Docetaxel (HR 0.60 95% CI, 0.48-0.74 p=0.0001) was noted without significant benefit in the Zoledronic Acid arm (HR 0.89 IC 95%, 0.73-1.07 p=0.221) even if patients are considered metastatic at the bone level [23]. Study CALGB92202 tested in 680 patients with castration-resistant metastatic prostate cancer; a castration +/- Zoledronic acid. There was no difference in the median occurrence of the first bone event between arm placebo 29.8 months and the acid arm Zoledronic 31.9 months with a random ratio, 0.97; 95% CI, 0 to 1.17 p=0.39 [24]. These data were consolidated in a meta-analysis that found no benefit in the addition of Zoledronic acid (0.94 [0 × 83-1 × 07], p=0.323) [25]. There are no data on data on denosumab.

Castration sensitive metastatic prostate cancer: Docetaxel or abiraterone plus androgenic suppression?

Several treatment options are available in castration-sensitive metastatic prostate cancer. However, no comparison between chemotherapy and new generation hormone therapy exists even in castration resistance castration. Nevertheless, these two molecules resulted in a similar benefit (HR 0.6) in overall survival and radiological progression-free survival (0.5) but a long follow-up with post-protocol analysis is necessary to see the long-term therapeutic effect (Table 1). In clinical practice, the choice between abiraterone and Docetaxel should consider the availability of drug, its route of administration (oral or intravenous), its cost and reimbursement, especially toxicity profile and patient preference. Patients eligible for Docetaxel must meet the criteria summarized in Table 2. Abiraterone should be used with caution in diabetic patients with cardiovascular risk. It is necessary to measure the arterial pressure of the patients and possibly to treat it and it is necessary to compensate the hypokalemia by the high potassium diet. However, studies comparing the quality of life under treatment (abiraterone versus Docetaxel) must be realized. But the question that arises today is that of the interest of adding a new generation hormone therapy to chemo-castration. Several ongoing European Peace (1 and 2) trials are ongoing. In our context, as an emerging country, given the frequency of metastatic stage disease and the cost these new treatments, we need to think about the castration method (medical or surgical) to offer to our patients and we need therapeutic sequence strategy testing to benefit our patients of all available molecules and prolong their survival while ensuring a better quality of life.

Future perspectives in castration sensitive metastatic prostate cancer

Several clinical ongoing trials are currently investigating potential novel potential therapeutic strategies in this disease setting. The combination approach, ongoing trials are evaluating the activity of alternative combinations of ADT and second-generation hormonal-therapy other than abiraterone, including enzalutamide (NCT02677896, NCT02446405, NCT03336983) and apalutamide (NCT02489318) (Figure 1). Furthermore, the early combination of chemo-castration plus second-generation hormonal-therapy (abiraterone acetate, or enzalutamide, or darolutamide) is of interest given the potential anti-tumour activity of simultaneous inhibition of androgen-dependent and independent pro-oncogenic pathways (NCT01957436, NCT03246347, and NCT02799602). Concerning sequential strategy, the TITAN trial is investigating the efficacy of apalutamide as maintenance therapy following Docetaxel (NCT02489318).

Conclusion

Castration sensitive metastatic prostate cancer (CSMPC) is a heterogeneous disease. Disease presentation and clinical course can vary broadly, ranging from indolent, oligometastatic disease, with lymph node metastases or minimal bone involvement, to aggressive forms with high tumour burden, visceral and/or extensive bone lesions. In this review, the treatment landscape of castration sensitive metastatic prostate cancer has been recently expanded. Androgenic suppression represents the cornerstone of (CSMPC) therapy. New effective molecules in resistance castration phase have shown their interest in sensitive castration phase. Combining androgen deprivation therapy with either Abiraterone or Docetaxel chemotherapy has been shown to significantly prolong overall survival compared with castration monotherapy in patients with high-risk metastatic disease and become standard of care. Zoledronic acid has no place. Choosing the right treatment for the right patient should consider patient preference, potential toxicities associated with Docetaxel and Abiraterone, as well as the cost of treatment.

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