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Mini Review

The Evolving Role of Chemotherapy in Prostate Cancer

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Abstract

Despite extensive clinical research of different chemotherapy agents for more than three decades, the role of chemotherapy in prostate cancer was only established in 2004, after demonstrating a survival benefit with docetaxel in metastatic castration resistant prostate cancer. Six years later, second line chemotherapy using cabazitaxel, after disease progression on docetaxel, demonstrated an additional survival improvement. Recently docetaxel given alongside standard hormonal therapy in newly diagnosed advanced prostate cancer cases was found to lead to significantly improved patient outcomes. This review aims to cover the role of chemotherapy in prostate cancer and the latest developments.

Keywords: Prostate cancer; Chemotherapy; Docetaxel; Cabazitaxel

Introduction

Prostate cancer is the most common malignancy in men in industrialized countries. Treatment options for localized prostate cancer include primary surgery (prostatectomy) or radical radiotherapy with or without Androgen Deprivation Therapy (ADT). ADT has traditionally been the mainstay of patients diagnosed with advanced prostate cancer. In the case of metastatic Castrate Resistance Prostate Cancer (mCRPC) major breakthrough shave been demonstrated in recent years using novel "hormonal" treatments such as abiraterone [1,2] and enzalutamide [3] but what is the role of chemotherapy in this disease? In this review, we will focus on the benefits and latest developments of chemotherapy in the treatment of advanced prostate cancer.

The way to the pacific yew tree

Up to 2004 the treatment of advanced prostate cancer was hormonal based and chemotherapy had a minor role in the treatment of patients with mCRPC. In the late 1980s and early 1990s chemotherapies such as 5-flurouracil (5-FU), cyclophosphamide and topotecan failed to show any benefit in mCRPC [4-6]. In 1996 Tannock and colleagues demonstrated palliative responses with mitoxantrone plus prednisone *vs.* prednisone only in a large randomized study [7], but yet again mitoxantrone gave no survival benefit for patients. A major shift though in our thinking about the role of chemotherapy in this disease came eight years later in 2004 with docetaxel. Docetaxel belongs to the Taxane family and is extracted from the pacific yew tree. Petrylak, et al. demonstrated survival superiority of docetaxel plus estramustine chemotherapy compared with mitoxantrone plus prednisone of about 2 months [8] and in the same year Tannock, et al. reported on the benefit of docetaxel plus prednisone *vs.* mitoxantrone plus prednisone in a large randomized trial, which included over a 1000 men with mCRPC. This landmark study (TAX 327) demonstrated that chemotherapy with Docetaxel improved patient's survival by almost 3 months. Data from the study suggested that 45% of patients achieved a reduction of upto 50% in the Prostate Specific Antigen (PSA) [9]. An update of this study in 2008 confirmed the survival advantage once again, as well as the improvement in quality of life and regardless of patients age [10].

Second line chemotherapy?

Based on the results of these studies, docetaxel became a standard of care in mCRPC and became an international standard of care. At the time there were no other approved treatments offering survival benefit in mCRPC. A number of subsequent trials failed to demonstrate a further benefit when combining docetaxel with other agents, these studies being criticised for being developed without clear biological rationale of the taxane-experimental agent combination. Drugs such as angiogenesis inhibitors and immunomodulators were amongst those studied. For example, Kelly, et al. reported on the addition of bevacizumab to docetaxel in a large randomized trial of men with mCRPC [11], but this trial failed to demonstrate improvement in survival. Petrylak, et al. reported a study in which lenalidomide, an immunomodulator as well as an angiogenesis inhibitor was added to docetaxel in mCRPC patients. This study was again negative [12].

In 2010, 6 years after Tannock, et al. demonstrated survival advantage with docetaxel, TROPIC and a multicentre international trial enrolled 755 patients with mCRPC after progression on docetaxel. Patients were randomized to receive cabazitaxel plus prednisone or mitoxantrone plus prednisone [13]. Cabazitaxel is a second generation taxane which overcomes the resistance developed with docetaxel. Patients on the cabazitaxel arm demonstrated improvement in overall survival of over 2 months with a reduction in mortality of 30%. This trail imprinted the role of cabazitaxel as a second line option after docetaxel in patients with mCRPC.

Following the survival benefit from cabazitaxel, further advances were achieved in the treatment of mCRPC. The novel hormonal agents abiraterone and enzalutamide showed improvement in survival in chemotherapy naive patients, as well as in the post docetaxel setting [2,14,15]. Survival benefits were also seen in mCRPC with sipuleucel-T, a dendritic based vaccine and radium 223, a radioactive alpha emitter [16,17]. Despite these encouraging results, a number of questions remain regarding the optimal sequencing of the newly available therapies. In this respect the identification of biomarkers to predict disease response would be hugely beneficial.

Androgen-sensitive metastatic prostate cancer

Hormonal treatment with ADT has traditionally been the main

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Table 1: Major studies of chemotherapy in advanced prostate cancer.

Author/Study	Year	Study design	End points
Tannock, et al. [7]	1996	Mitoxantrone plus prednisone *vs.* prednisone (in patients with mCRPC)	Palliative response (pain control) of 29% with Mitoxatrone *vs.* 12% with prednisone
Tannock, et al. [9]	2004	Docetaxel 75mg/m^2 Q3weeks *vs.* Docetaxel 30mg/m^2 weekly *vs.* Mitoxantrone in mCRPC (all arms received prednisone)	OS: 19.2 Mo. *vs.* 17.8 Mo. *vs.* 16 Mo. (p= 0.009 for Docetaxel 75mg/m^2)
De Bono, et al. [13] (TROPIC)	2010	Cabazitaxel 25mg/m^2 Q3weeks plus prednisone *vs.* mitoxatrone plus prednisone for mCRPC patients who advanced on docetaxel	PFS: 2.8 Mo. *vs* 1.4 Mo. OS: 15.1 Mo. *vs.* 12.7 Mo. (p= 0.001)
Gravis, et al. [19] (GETGU-AFU-15)	2013	Docetaxel 75mg/m^2 Q3weeks plus ADT *vs.* ADT alone in castrate sensitive patients	MOS: 58.9 Mo. *vs.* 54.2 Mo. (p= 0.955)
Sweeney, et al. [20] (CHAARTED)	2014	Docetaxel 75mg/m^2 Q3weeks plus ADT *vs.* ADT alone in newly diagnosed patients with metastatic castrate sensitive cancer	OS: 57.6 Mo. *vs.* 44 Mo. (p= 0.0003)
James, et al. [21] (STAMPEDE)	2015	Docetaxel 75mg/m^2 Q3weeks plus SOC *vs*. SOC in locally advanced and metastatic castrate sensitive prostate cancer	MOS: 81 Mo. *vs*. 71 Mo. (p= 0.006)

ADT: Androgen-Deprivation Therapy; mCRPC: metastatic Castration-Resistant Prostate Cancer; OS: Overall Survival; MOS: Median Overall Survival; SOC: Standard of Care

stay of treatment for patients with advanced or metastatic castration sensitive prostate cancer. But what if chemotherapy was introduced in this stage of disease, before the inevitable development of hormone resistance? Several studies addressed this specific question. Milikan, et al. failed to demonstrate survival benefit or delay in the appearance of castration resistant disease with the use of ketoconazole and doxorubicin alternating with vinblastine chemotherapy [18]. The GETGU-AFU-15 reported by Gravis, et al. was a randomised trial exploring the approach of upfront docetaxel with ADT in newly diagnosed metastatic castrate sensitive disease. No significant improvement in survival was reported with docetaxel [19]. In 2014 the CHAARTED trial marked a dramatic change in the approach towards metastatic castration sensitive disease by demonstrating a significant improvement in survival of patients receiving docetaxel chemotherapy (6 cycles) with ADT *vs.* ADT alone [20]. Patients on the chemotherapy arm had an improvement in median overall survival of 13.6 months with an acceptable toxicity profile. Moreover, patient with "high-volume" metastatic disease had an improvement of 17 months in their median survival.

Further to CHAARTED, James and colleagues presented in 2015 the results of the chemotherapy arms of the STAMPEDE phase III randomized trial in locally advanced and metastatic prostate cancer, showing an improvement in median overall survival of 10 months with a hazard ratio of 0.78 in favour of the patients receiving 6 cycles of docetaxel chemotherapy with daily prednisone in addition to ADT, along with a significant improvement in time to progression. Patients specifically with metastatic disease had a greater overall survival benefit [21] (Table 1).

Conclusion

For many years prostate cancer was regarded as a chemotherapy-insensitive disease. However, the role of chemotherapy in prostate cancer has significantly evolved in the last decade from a palliative treatment into a therapy to be given as an adjunct to ADT in hormone sensitive disease which can improve dramatically the survival of patients. These findings are highly relevant clinically particularly as such large differences in survival are relatively unprecedented in solid tumour oncology. These impressive results also raise the question of the potential role of chemotherapy in localized prostate cancer as an adjunct to primary radical surgery and/or radiotherapy.

Study groups are continuing to explore the addition of various biological agents to chemotherapy. For example, the effect of combining a Dendritic Cell Vaccine (DCVAC) with docetaxel is currently being tested in a large international phase III trial (VIABLE). The idea of combining a vaccine with chemotherapy is based on the results of the IMPACT study which showed that a vaccine based treatment with sipuleucel-T, an immunostimulant vaccine, improves the survival of patients with mCRPC [16]. In addition, adjuvant treatment with docetaxel in high risk prostate cancer is still under investigation with conflicting results. For example, Sandler, et al. presented data regarding adjuvant treatment with docetaxel after radiotherapy (RTOG 0521 study) at the American Society of Clinical Oncology (ASCO) in 2015, showing an absolute benefit in overall survival of 4% and a reduction of 30% in risk of death in favour of adjuvant docetaxel. On the other hand, a number of trials including the RTOG 9902 phase 3 trial addressing the same question did not see any clear benefit from adjuvant docetaxel in terms of overall survival [22,23].

In summary, chemotherapy is an important element in the treatment of advanced prostate cancer and is becoming the standard of care also in castration sensitive disease, and maybe even in high-risk for recurrence prostate cancer. It is expected that chemotherapy will play an even more prominent role in prostate cancer in the near future and will serve as a backbone for new evolving therapeutic approaches.

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