Cancer Treatment Reviews 41 (2015) 247–253

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Anti-Tumour Treatment

Enzalutamide: A new prostate cancer targeted therapy against the androgen receptor

Martín Lázaro Quintela [c,2], Luis León Mateos [d,3], Sergio Vázquez Estévez [a,*], Ovidio Fernández Calvo [f,5], Urbano Anido Herranz [e,4], Francisco Javier Afonso Afonso [g,6], Lucía Santomé [b,1], Luis Antón Aparicio [h,7]

[a] Servicio de Oncología Médica, Hospital Universitario Lucus Augusti, C/Doutor Ulises Romero, s/n, 27003 Lugo, Spain
[b] Servicio de Oncología Médica, Hospital Povisa, C/Salamanca 5, 36211 Vigo, Spain
[c] Oncología Médica, Complexo Hospitalario Universitario de Vigo, C/Pizarro 22, 36204 Vigo, Spain
[d] Servicio de Oncología Médica, Complexo Hospitalario Universitario de Pontevedra, Spain
[e] Oncología Médica, Complejo Hospitalario Universitario de Santiago de Compostela, c/Choupana s/n, 15706 Santiago de Compostela, A Coruña, Spain
[f] Servicio Oncologia Medica, Complejo Hospitalario Universitario Ourense, C/Ramón Puga 54.32005, Spain
[g] Oncología Médica, C.H.U.Ferrol, Ferrol, A Coruña, Spain
[h] Medical Oncology Service, CHUA Coruña, Spain

ARTICLE INFO

Article history:
Received 22 September 2014
Received in revised form 11 December 2014
Accepted 12 December 2014

Keywords:
Enzalutamide
Metastatic castration-resistant prostate cancer
Abiraterone
Cabazitaxel
Docetaxel

ABSTRACT

Enzalutamide (MDV3100), an androgen receptor-signalling inhibitor, represents the most recent compound added to the therapeutic armamentarium for the treatment of metastatic castration-resistant prostate cancer (mCRPC) who progressed to docetaxel. The anti-tumour activity and safety of enzalutamide has been demonstrated in a phase III clinical trial, showing a benefit in overall survival, which was the primary endpoint. There are no head-to-head studies comparing the different treatment options in this subset of patients. In this article, most relevant data published in the literature have been reviewed, with special attention to the therapeutic alternatives currently available for postdocexatel mCRPC patients, emphasising the mechanisms of action of the different drugs, efficacy and quality of life-related aspects.

Introduction

Docetaxel combined with prednisone is currently the treatment of choice in patients with disseminated castration-resistant prostate cancer (CRPC). The option of docetaxel plus prednisone in advanced CRPC was approved in 2004 after publication of two independent phase III randomised studies showing an improvement in overall survival and quality of life in this group of patients [1,2]. Thereafter, a better knowledge of the mechanisms of resistance and androgen production-related signalling pathways made possible the synthesis of new drugs with different mechanisms of action, including chemotherapeutic agents (cabazitaxel) [3] and agents with anti-androgenic activity (abiraterone acetate and enzalutamide) [4–6], all of which have demonstrated an increase in survival after disease progression on docetaxel.

This article presents a review of the different mechanisms of action of these drugs, with a particular focus on enzalutamide (MDV3100) because of its pharmacological characteristics, toxicity profile and health-related quality of life benefits in patients with prostate adenocarcinoma who had been treated with docetaxel.

Comparative analysis of the mechanisms of action

The development of CRPC is characterised by progression of the disease despite serum testosterone levels in the range of castration. There is increasing evidence of CRPC dependence on the androgen-receptor (AR) signalling pathway and underlying mechanisms. Androgen receptor expression is maintained

* Corresponding author. Tel.: +34 982295106.
E-mail addresses: martin.lazaro.quintela@sergas.es (M.L. Quintela), luis.leon.mateos@sergas.es (L.L. Mateos), sergio.vazquez.estevez@sergas.es (S.V. Estévez), ovidiofernandezcalvo@yahoo.es (O.F. Calvo), urbanoanido@gmail.com (U.A. Herranz), Francisco.Javier.Afonso.Afonso@sergas.es (F.J.A. Afonso), lsantome@povisa.es (L. Santomé), luis.anton.aparicio@sergas.es (L.A. Aparicio).
[1] Tel.: +34 9864131441333.
[2] Tel.: +34 986219766/609110419.
[3] Tel.: +34 986807101.
[4] Tel.: +34 981950544/630050938.
[5] Tel.: +34 988385500 649196690.
[6] Tel./fax: +34 981334034.
[7] Tel.: +34 981 178 107.

http://dx.doi.org/10.1016/j.ctrv.2014.12.006
0305-7372/

throughout prostate cancer progression. Adrenal and intra-tumour androgens are an important source of AR activation. Other mechanisms resulting in permanent activation of AR include amplification and overexpression of the AR gene, AR mutations reducing ligand-binding specificity, activation of alternative Ras/Raf/MEK/ERK or Src and Ack1 thyrosine kinase pathways, altered levels of proteins promoting co-activation of AR and constitutively active AR splice variants [7].

The taxanes are microtubule-stabilising agents. Microtubules, key components of the cytoskeleton, are crucial in the development and maintenance of cell shape, in the transport of vesicles, traffic of transcription factors, mitochondrial function, cell signalling and cell division and mitosis. Taxanes are known to have a role in the separation of chromosomes during mitosis preventing transition from metaphase to anaphase and promoting apoptosis [8,9]. Also, taxanes inhibit anti-apoptotic function of the Bcl-2 family proteins [9,10] and activate cyclin-dependent kinase inhibitor 1A (p21, Cip1) and p53 protein in cancer cells causing cell cycle arrest and apoptotic cell death [11]. Taxanes may also have a direct effect on androgenic signalling pathway in prostate cancer. The microtubule stabilising activity of taxanes leads to AR cytoplasmic sequestration and subsequent inhibition of transcription activity in response to androgens or other ligand-independent pathways [12,13]. In addition, it has been shown that taxanes induce nuclear accumulation of FOXO1, which is a known AR suppressive nuclear factor [14]. It is possible that taxane inhibition of the AR signalling pathway may be more relevant than the anti-mitotic activity, which may explain why taxanes are the only chemotherapeutic agents with a beneficial effect on survival in prostate cancer. Cabazitaxel overcomes one of the mechanisms of resistance of other taxanes due to poor affinity for the p-glycoprotein drug efflux pump, a major mechanism of resistance to docetaxel [12].

Abiraterone, the active metabolite of abiraterone acetate, is an irreversible inhibitor of CYP17A1 [15], the 17α-hydroxilase and $C_{17,20}$-lyase enzymatic activity of which is essential for androgen biosynthesis [16]. Pregnenolone and progesterone are converted to 17α-hydroxipregnenolone and 17α-hydroxiprogesterone by the 17α-hydroxilase activity of CYP17A1, and then to dehydroepiandrosterone (DHEA) and androstenodione by $C_{17,20}$-lyase activity. DHEA and androstenodione are precursors of testosterone [16]. CYP17A1 is expressed in testicular, adrenal and prostate tumour tissue. The expression of CYP17A1 in castration-resistant metastases has been reported to be 16.9 times higher than in the primary tumour [17]. Abiraterone requires the concurrent use of low-dose corticosteroids to inhibit ACTH stimulation and subsequent increase of mineralocorticoids and prevent secondary effects, such as fluid retention, hypokalemia and hypertension.

Enzalutamide has a much higher affinity for the AR receptor than first-generation antiandrogens [7], with no agonist activity and demonstrates activity even in case of amplification and overexpression of the AR, which are well known mechanisms involved in androgenic castration resistance [18]. Enzalutamide inhibits the AR signalling pathway and is a competitor inhibitor of dihydrotestosterone (DHT), the active metabolite of testosterone. In contrast to first-generation antiandrogens, enzalutamide also inhibits nuclear translocation of DHT-AR complex, remaining a significant fraction of AR in the cytoplasm and interfering directly in AR-mediated DNA transcription [18]. This clear differentiating mechanism results in a reduction of prostate cancer cell proliferation and an increase in cell death. Enzalutamide has also shown activity in AR splice variants lacking the ligand binding domain, a further known mechanism of castrate resistance, although detection of AR-V7 in circulating tumour cells may be associated with resistance to enzalutamide and abiraterone [19]. Therefore, in contrast to the ligand-dependent activity of abiraterone (adrenal and intratumoral residual androgens) in CRPC, enzalutamide acts on ligand-dependent resistance mechanisms (AR amplification) as well as ligand-independent resistance mechanisms (AR splice variants) (Fig. 1).

Unlike abiraterone, concomitant steroids are not needed because enzalutamide lacks the detrimental effects of mineralocorticoids excess.

Despite the different mechanisms of action of enzalutamide and abiraterone, there is some scientific evidence of a possible interaction between taxanes and hormonal therapy based on preclinical data suggesting that androgen ablation, although effective in the control of the prostate tumour size, may increase the possibility of metastases and castration resistance by promoting epithelial mesenchymal transition (EMT) [20]. Androgen deprivation also increases ZEB1 transcription factor levels, a direct regulator of EMT related to taxane resistance [21].

Clinical data mostly based on retrospective studies with a small number of patients also indicate that androgen-deprivation therapies may reduce the efficacy of subsequent treatments with taxanes [22–24]. Studies suggesting a possible cross resistance between enzalutamide and abiraterone are also retrospective with a limited number of patients [25,26].

Clinical development of enzalutamide

Before the use of enzalutamide in phase I–II studies, the effect of this drug was studied on CRPC xenograft models. Enzalutamide showed the ability to inhibit AR signalling in the overexpression of AR cells with high binding affinity to the AR and lack of agonist activity [18,27]. Enzalutamide bound to the AR in a castration-resistant LNCaP/AR human prostate cancer cell model showing an eight-fold greater affinity than bicalutamide. Also, enzalutamide induced regression of established LMCaP/AR xenograft tumour cells, which overexpress ARs growing in castrated male mice [18,27]. These data demonstrated the activity of enzalutamide and allowed the development of subsequent clinical studies.

A phase I–II study was conducted by Scher et al. [28] to assess the antitumour activity and efficacy of enzalutamide in patients with progressive metastatic CRPC (mCRPC). In this study, 140 patients were enrolled in dose-escalation cohorts of 3-6 patients starting with 30 mg dose. The final doses studies were 30 mg ($n = 3$), 60 mg ($n = 27$), 150 mg ($n = 28$), 240 mg ($n = 29$), 360 mg ($n = 28$), 480 mg ($n = 22$) and 600 mg ($n = 3$). Decreases in prostate specific antigen (PSA) levels were seen at all doses, in both chemotherapy-naïve and chemotherapy-treated patients, with a PSA decline of 50% or more in 56% of patients. Partial responses were observed in 13 (22%) out of 59 patients with soft tissue metastases. The median time to radiological progression was 47 weeks. The maximum tolerated dose was 240 mg, with fatigue as the most frequent adverse event (grade 3–4 in 11% of patients). The subsequent lower level (150 mg) was established as the dose to be used in further studies, although the final commercialised dose was 160 mg. This study also assessed AR binding *in vivo* in 22 patients using 16 beta[18F]-fluoro-5 alpha-dihydrotestosterone (FDHT) positron emission tomography (PET) scans to measure change in FDHT uptake before and after starting treatment. All patients showed a clear reduction in FDHT uptake (range approximately ~20–100%).

In the landmark phase III, double-blind, placebo-controlled AFFIRM (A Study Evaluating the Efficacy and Safety of the Investigational Drug MDV3100) trial [6], 1199 men with castration-resistant prostate cancer with $\leqslant 2$ prior chemotherapy regimens, including $\geqslant 1$ containing docetaxel, were randomly assigned in a 2:1 ratio, to receive oral enzalutamide at a dose of 160 mg per day (800 patients) or placebo (399 patients). Corticosteroids administration was optional in both arms. At a planned interim analysis after 520 death events, enzalutamide was superior to