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CASE REPORT

Cabazitaxel in castration resistant prostate cancer with brain metastases: 3 case reports

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Abstract

Prostate cancer is the most common non-cutaneous malignancy for men. The skeleton is the most common metastatic site but, following an improvement in survival, metastases in uncommon sites are being found more frequently in clinical practice, especially brain metastases. Despite the new drugs now available for metastatic castration resistant prostate cancer, no clinical evidence exists about their effectiveness on brain metastases. We describe the clinical history of 3 patients treated with cabazitaxel plus whole brain radiotherapy. These case reports demonstrate that cabazitaxel is highly active and well tolerated in brain metastases.

Key words: Cabazitaxel; Brain metastases; Prostate cancer

Core tip: Due to the improvement in terms of survival, the incidence of brain metastases (BMs) has increased in patients with metastatic castration resistant prostatic cancer (mCRPC). Despite the large number of treatments now available, the prognosis of patients with BMs is still poor. First, we demonstrate the efficacy of cabazitaxel on brain mestastases in three CRPC patients and then show its profile of tolerability in combination with whole brain radiotherapy.

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INTRODUCTION

Prostate cancer (PC) is the most common non-cutaneous malignancy for men, with an estimated number of new cases of 241740 in 2013 in the United States[1]. Nevertheless, PC is not the leading cause of death in the male population due to its ability to rarely metastasize to organs other than bones[2].

Although the skeleton remains the most common metastatic site, the availability of new active drugs for metastatic castration resistant prostatic cancer (mCRPC) has changed the natural history of this disease, leading to a considerable improvement in survival so that metastases in previously considered uncommon sites are now found more frequently[3].

Brain is the site of metastases in almost 12% of cases with a poor prognosis at their appearance[4].

Despite an increased incidence of BMs, the impact of new drugs for mCRPC on this metastatic site remains poorly understood. First of all, patients with BMs are not routinely enrolled in phase Ⅲ clinical trials and there are

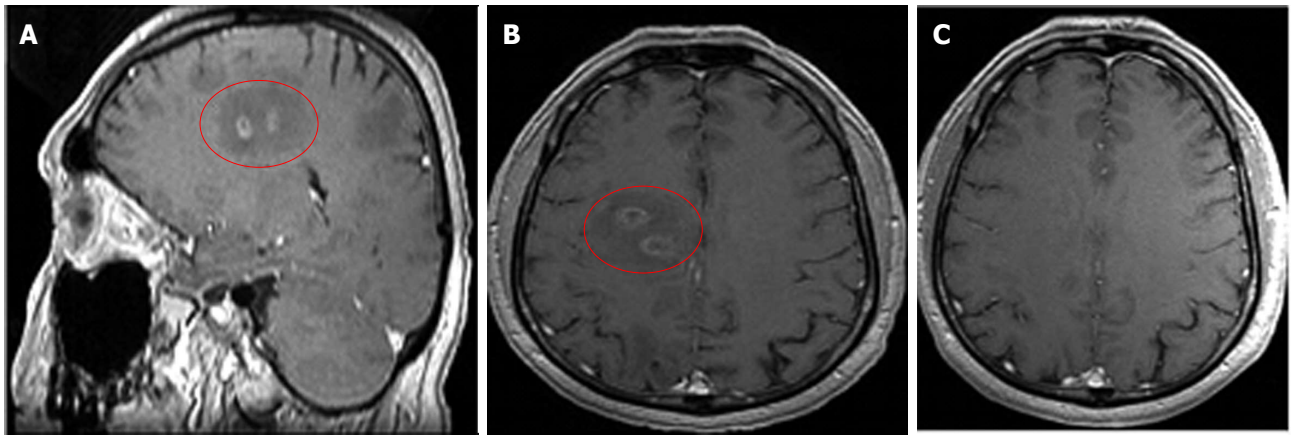

Figure 1 Show a complete response in the brain lesions before and after 6 cycles of cabazitaxel. A, B: Brain metastases before cabazitaxel; C: Complete response after 6 cycles of cabazitaxel.

no prospective and ad-hoc studies in this particular setting. Actually, there is only preclinical data showing that cabazitaxel is able to pass the brain-blood barrier (BBB)[5] but no evidence about its efficacy in humans.

Otherwise, there is also little data concerning the role of radiation therapy on the treatment of BMs from PC which seems to have only a palliative intent[6]. Here, we describe three case reports of brain metastases in CRPC patients who were treated with cabazitaxel plus whole brain radiotherapy.

CASE REPORT

The patients were 70, 70 and 72 years old. All patients presented at diagnosis with a high risk disease (Table 1). Patients 1 and 2 did not receive primary treatment because bone metastases and lymph node metastases were detected with bone and computed tomography scans. These 2 patients began hormonal therapy with luteinizing hormone releasing hormone analogue (aLHRH) first and then with complete androgen blockage (CAB), adding bicalutamide 50 mg.

Patient 3 underwent prostatectomy and radiotherapy for locally advanced disease. The disease progressed after 5 mo due to the appearance of bone metastases and aLHRH was started. All patients had a long androgen deprivation therapy (ADT) history (36-50 mo). Docetaxel was first line chemotherapy with a progression free survival (PFS) of 7, 7 and 11 mo respectively (Table 1). Patient 3 was treated with abiraterone as second line treatment and progressed after 6 mo.

The patients presented with multiple BMs (in number, 2, 3 and 3 respectively) confirmed with a magnetic resonance imagining (MRI) before starting cabazitaxel and the liver and lung were the other metastatic sites (Table 1). A total of 30 cycles of cabazitaxel were administered at standard dose without reductions (Table 1). Contemporaneous whole brain radiotherapy was performed at the dose of 30 Gy.

Patient 3 obtained a complete response on brain and liver metastases with a PSA reduction of 90% after 6 cycles (Figure 1), while two partial responses in brain (the lesions were halved) and lung were observed, with a PSA decrease of 40% after 6 cycles for patient 1 and 2.

No grade 3-4 toxicities were experienced; all patients received pegylated granulocyte colony stimulating factor (PEG-G-CSF) to prevent febrile neutropenia. The most important non-hematological toxicities were grade 2 nausea and asthenia.

The PFS of patients 1 and 2 was 7 and 13 mo while patient 3 is still progression-free. Patients 1 and 2 received further therapy after cabazitaxel (abiraterone and platinum regimen) and died after 3 mo.

DISCUSSION

BM appearance is a rare and terminal event in the natural history of PC due to greater aggressiveness and poor response to common therapies. BMs are often essentially single, supratentorial and occur with nonfocal neurological symptoms related to intracranial hypertension. A retrospective study of 103 patients with BMs showed that radiotherapy alone is an effective treatment with a median survival of 3.5 mo[7].

Further improvement in survival was noted in five patients who underwent stereotactic radiosurgery (SRS). Although no complete responses were obtained, symptoms improved[8].

BMs are more frequent in the CRPC setting than in the past due to the availability of new drugs and longer survival of metastatic patients. In the docetaxel era, the prognosis of patients with BMs was still poor and median survival was only 8 weeks after BM diagnosis, demonstrating the clinical ineffectiveness of docetaxel[3].

Among the new approved drugs for mCRPC, such as cabazitaxel, abiraterone, enzalutamide and sipuleucel-T, only cabazitaxel has been shown to be able to pass the BBB. Cisternino and colleagues observed a non-linear accumulation of cabazitaxel in the brains of rats, occurring by saturation of the P-glycoprotein in the BBB[5].

Table 1 Patient characteristics

	Patient 1	Patient 2	Patient 3
Age (yr)	70	70	72
Comorbidities	Hypertension	Hypertension	Diabetes
Primary treatment	Hormonal therapy	Hormonal therapy	Surgery and radiation therapy
Gleason score	8 (4 + 4)	8 (4 + 4)	8 (5 + 3)
PSA at baseline[1] (ng/mL)	158	82	17
ADT time (mo)	38	36	50
Docetaxel cycles	12	8	8
PSA pre-cabazitaxel (ng/mL)	95	292	140
Sites of metastases	Bone, lung, brain	Bone, lung, brain	Bone, liver, brain
Cabazitaxel cycles	12	8	10
Best response	PR on brain and lung	PR on brain and lung	CR on liver and brain
Toxicities	Anemia grade 1, asthenia grade 2	Nausea grade 2; neutropenia grade 2	Asthenia grade 2

[1]Before primary treatment. ADT: androgen deprivation therapy; PR: Partial response; CR: Complete response.

These 3 case reports describe the role of cabazitaxel in patients with BMs for the first time and the results are encouraging for 3 reasons.

Firstly, it shows the definite efficacy of cabazitaxel in BMs with an amazing PFS compared with the Tropic trial PFS[9]. Secondly, the association of whole brain radiotherapy and chemotherapy with cabazitaxel gives better results in terms of radiological response and survival than the data presented above.

Thirdly, the combination does not seem to be particularly toxic, especially in terms of hematological toxicities. We administered preventive PEG-G-CSF and, as previously shown in an Italian study, it reduced the grade 3 and 4 neutropenia reported with cabazitaxel[10]. Of note, all three patients had a gleason 8 at diagnosis, which is consistent with our previosly reported findings suggesting improved PFS in patients with high gleason score receiving cabazitaxel[11].

Our case reports demonstrate that cabazitaxel improved PFS and overall survival in our patients with BMs and is well tolerated in combination with we decided to report these cases in a full paper without presenting them as a meeting abstract, considering that only 50% of abstracts are subsequently published as full papers[12]. The lack of ad-hoc studies and the exclusion of men with brain metastases from phase Ⅲ trials make our data the first evidence in this field. Prospective trials are needed to confirm our preliminary results.

COMMENTS

Case characteristics

All patients presented at diagnosis with a high risk disease.

Treatment

The authors demonstrate the efficacy of cabazitaxel on brain metastases in three castration resistant prostatic cancer patients and show its profile of tolerability in combination with whole brain radiotherapy.

Experiences and lessons

These case reports demonstrate that cabazitaxel is highly active and well tolerated in brain metastases.

Peer review

Nice, well written paper with interesting data potentially useful in the clinical setting.

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