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

Rescigno P *et al*. Cabazitaxel and brain metastases

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**Abstract**

Prostate cancer represents the most common non-cutaneous malignancy for men. Skeleton is the most common metastatic site but, following an improvement of survival, metastases in uncommon sites are found more frequently in clinical practice, especially brain metastases. Despite new drugs, now available for metastatic castration resistant prostate cancer, no clinical evidence exists about their effectiveness on the brain metastases. We describe 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.

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**Key words**: Cabazitaxel; Brain metastases; Prostate cancer

**Core tip:** Due to the improvement in term of survival, the incidence of brain metastases (BMs) has increased in patient with metastatic castration resistant prostatic cancer (mCRPC). Despite a 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 show its profile of tolerability in combination with whole brain radiotherapy.

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**INTRODUCTION**

Prostate cancer (PC) represents 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 first cause of death in male population due to its ability to metastasize rarely to organs that are not the 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 involved as site of metastases in almost 12% of cases and the prognosis of the patients is poor at their appearance[4].

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

Otherwise we have also few data concerning the role of radiation therapy on the treatment of BMs from PC and it 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 a high risk disease (Table 1). Patients 1 and 2 didn’t receive primary treatment because bone metastases and lymph node metastases were detected with bone and computed tomography scan. 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. Then he experienced a disease progression after 5 mo due to bone metastases appearance and started aLHRH. 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 months respectively (Table 1). Patient 3 was treated with abiraterone as second line treatment and progressed after 6 mo.

The patients presented multiple BMs (in number of 2, 3 and 3 respectively) confirmed with a magnetic resonance imagining (MRI) before starting cabazitaxel, liver and lung represented 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-haematological toxicities were grade 2 nausea and asthenia.

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

**DISCUSSION**

BMs 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 neurologic symptoms related to intracranial hypertension. A retrospective study about 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). No complete responses were obtained, however best improvement regarded symptoms[8].

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

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

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

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

Thirdly the combination seems not be particularly toxic, especially in terms of hematological toxicities. We have administered preventive PEG-G-CSF and, as previously shown in an Italian study, it reduces the grade 3 and 4 neutropenia reported with cabazitaxel[10].

Our case reports demonstrate that cabazitaxel has improved PFS and overall survival in our patients with BMs and it is well tolerated in combination with radiotherapy. 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 a high risk disease.

***Treatment***

The authors demonstrate the efficacy of cabazitaxel on brain mestastases in three CRPC 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 interest data potentially useful in clinical setting.

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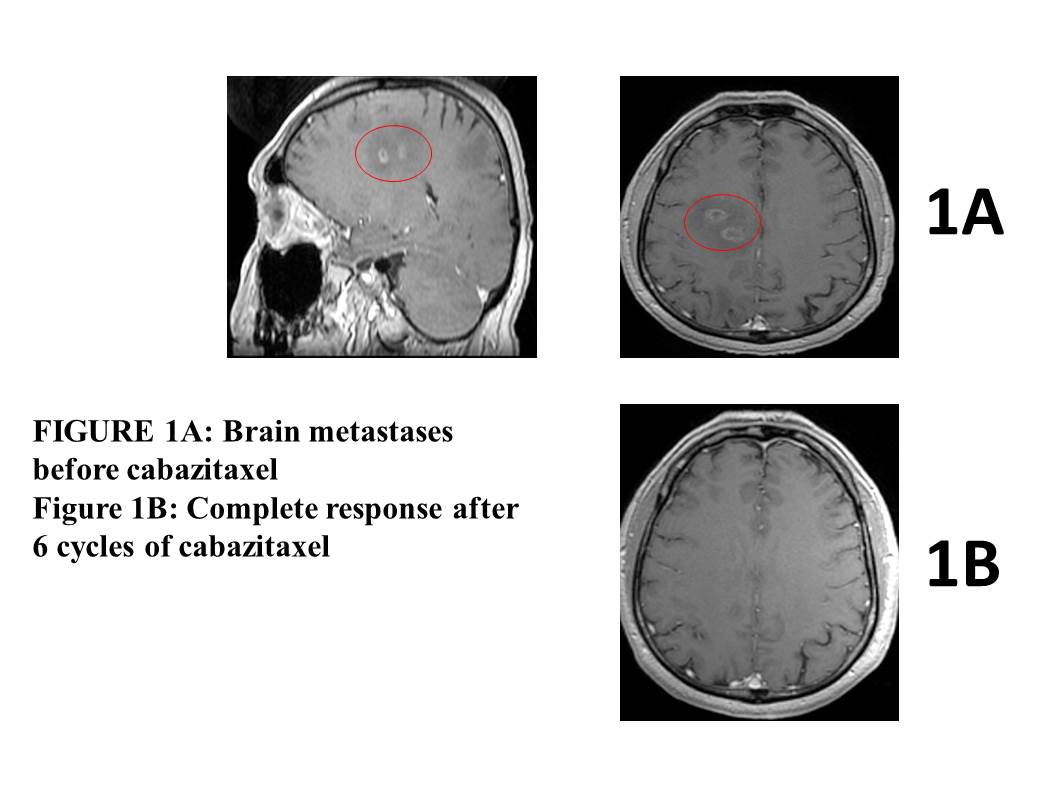
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**Figure 1 A and B show a complete response in the brain lesions before and after 6 cycles of cabazitaxel.**

**Table 1 Patient’s characteristics**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Patient 1** | **Patient 2** | **Patient 3** |
| Age | 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 baseline1 (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 |

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