CASE REPORT
Headache Caused by Brain Metastases of Castration-resistant Prostate Cancer during Cabazitaxel Therapy

Keitaro Watanabe, Takeo Kosaka, Hiroshi Hongo, Satoshi Tamaki and Mototsugu Oya

Department of Urology, Keio University School of Medicine, Tokyo, Japan

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We describe the case of a 55-year-old man who underwent four cycles of cabazitaxel therapy for castration-resistant prostate cancer (CRPC). After the fourth cycle of cabazitaxel, the patient experienced severe headaches. Brain gadolinium (Gd) contrast-enhanced magnetic resonance imaging (MRI) revealed multiple brain metastases. A few days later, the patient suffered impaired consciousness that progressed rapidly. The patient was treated for the symptoms of increased intracranial pressure and underwent whole-brain radiation. One month later, the patient’s consciousness level and headache had improved.

Although brain metastases of prostate cancer are rare, the possibility of brain metastases should be considered for prostate cancer patients, especially when a CRPC patient complains of headache. Additionally, even if major conditions such as cerebral hemorrhage are excluded by the use of non-contrast-enhanced computed tomography, brain Gd contrast-enhanced MRI should be performed in consideration of the possibility of brain metastases of prostate cancer. (doi: 10.2302/kjm.2016-0014-CR)

Keywords: prostate cancer, cabazitaxel, headache, brain metastases, gadolinium contrast-enhanced MRI

Introduction
Brain metastases of prostate cancer are rare. In the follow-up of prostate cancer, brain metastases are not routinely searched for. There have been no reports of brain metastases being diagnosed during cabazitaxel therapy for castration-resistant prostate cancer (CRPC). Cabazitaxel is a tubulin-binding taxane drug that can easily cross the blood–brain barrier (BBB). A phase 3 trial demonstrated improved overall survival in patients with CRPC after and during docetaxel-containing therapy.1 We report on the presence of brain metastases that triggered headache in a CRPC patient treated with cabazitaxel. Gadolinium (Gd) contrast-enhanced magnetic resonance imaging (MRI) was required to detect the metastases.

Case presentation
The case of a 55-year-old man with a history of prostate cancer is described. In 2012, the patient presented with back pain to the internal medicine department at another hospital. Contrast-enhanced computed tomography (CT) revealed irregular enlargement of the prostate and bone sclerosis of the vertebral bodies, pelvic bone, and femoral bone. Prostate-specific antigen (PSA) levels were elevated at more than 1000 ng/ml. Prostate cancer and multiple bone metastases were suspected. Transrectal prostate needle biopsy was performed, and the patient was diagnosed with Gleason score 4+4 and cT3aN0M1 prostate cancer. He was treated with combined androgen blockade therapy and denosumab for the bone metastases. He responded well to the treatment (PSA nadir of 0.31 ng/ml). After 10 months, the patient was diagnosed with
CRPC because of increasing PSA levels. Three cycles of docetaxel were administered and resulted in an 80% reduction in PSA. However, after 3 months of docetaxel treatment, the PSA level again became elevated. Despite sequential use of enzalutamide and abiraterone, the PSA level reached 551.04 ng/ml. Consequently, the patient was started on cabazitaxel therapy. After four cycles of cabazitaxel, PSA levels had responded well (39.47 ng/ml).

Fig. 1 shows the timeline of treatment and levels of PSA and alkaline phosphatase (ALP). Bone scintigraphy and contrast-enhanced CT of the chest, abdomen, and pelvis established no new findings. Although the fifth cycle of cabazitaxel was scheduled, the patient presented to our hospital because of severe headache and nausea. Neither non-contrast-enhanced brain CT [which ruled out cerebral hemorrhage, hydrocephalus, and herniation (Fig. 2A)] nor neurological examination could reveal the cause of the severe headache. We suspected the presence of brain metastases, so we performed Gd contrast-enhanced MRI. Many deeply stained nodules were found in the brain, the leptomeninges, and the skull on Gd contrast-enhanced T1-weighted imaging (T1WI) (Fig. 2C, D). We consulted neurosurgeons and they concluded that the headache and nausea were caused by increased intracranial pressure resulting from brain metastases. Subsequently, the patient’s level of consciousness decreased (Glasgow Coma Scale: GCS E1V2M1), so we administered mannitol, furosemide, and dexamethasone to reduce intracranial pressure. Simultaneously, we started whole-brain radiation (30 Gy/10 fractions). After 1 month, the patient’s level of consciousness recovered (GCS E4V5M6) and the headache was ameliorated. However, the Eastern Cooperative Oncology Group Performance Status Score decreased to 4, and we decided to cease cabazitaxel therapy. The patient was transferred to a different hospital for the continuation of rehabilitation.

Discussion

Brain metastases of prostate cancer

According to previous studies, the incidence of brain metastases of prostate cancer ranged between 0.16% and 3.3%. The mean age at the detection of brain metastases ranged from 61.3 to 68.8 years. Initial symptoms often result from increased intracranial pressure and diffuse cortical disorder and include delirium (51%), headache (36%), and memory deficits (17%). Clinically, brain metastases present with signs of increased intracranial pressure (headache, nausea, and vomiting), changes in mental status, seizures, or focal signs. Overall, 95% of patients with brain metastases of prostate cancer had concurrent osseous metastases. The mean overall survival after diagnosis of brain metastases of prostate cancer ranged from 1 to 9.2 months. In cases where brain metastases were treated, the mean overall survival ranged from 3.5 to 9.2 months.
brain metastases ranged from 21.9 to 45.6 months.\textsuperscript{4,6,8,9}

We performed a literature search for reports on intracranial metastasis of prostate cancer published after 2000. The detailed treatment course was obtained for eight cases\textsuperscript{11–18} in which the brain metastases were sensitive to hormonal therapy. Moreover, 23 cases (18 reports)\textsuperscript{19–36} of intracranial metastasis of CRPC were identified. To clarify the characteristics of intracranial metastases of CRPC, these 23 cases are reviewed in Table 1. We excluded cases in which CRPC was not clearly evident before the detection of brain metastases and cases of metastases in the skull base only. In the 23 cases reviewed, the Gleason score ranged from 5 to 10 and the mean age was 69.6 (55–79) years. Of the 23 cases, 11 featured multiple metastases. In cases for which death was confirmed, the overall survival time from the detection of brain metastases ranged from 3 days to 16 months. However, for cases in which brain metastasis were treated, the mean overall survival was 4.8 months (from 3 weeks to 16 months).

The frequency of brain metastases of prostate cancer is low. However, regardless of the length of time from the diagnosis of prostate cancer, brain metastases should be

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig2.png}
\caption{(A) Non-contrast-enhanced CT, (B) non-contrast-enhanced MRI T1-weighted image (T1WI), (C) gadolinium (Gd) contrast-enhanced MRI T1WI, (D) coronal slice of Gd contrast-enhanced MRI T1WI. Gd contrast-enhanced T1WI revealed metastases on both sides of the cerebellum (arrows). (D) shows leptomeningeal metastases (arrowhead, arrow). (A, B) are the same slices as (C) and revealed no abnormal lesions.}
\end{figure}
Table 1. Summary of intracranial metastases of CRPC reported after 2000

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Gleason score</th>
<th>Age (years)</th>
<th>Brain metastases: solitary or multiple</th>
<th>Concurrent metastases</th>
<th>Treatment for intracranial metastases</th>
<th>Survival after treatment for intracranial metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martin, V et al.</td>
<td>2015</td>
<td>3+5</td>
<td>66</td>
<td>Unknown</td>
<td>Bone, iris, skin</td>
<td>Carboplatin, docetaxel, and whole-brain radiation (30 Gy)</td>
<td>1 month</td>
</tr>
<tr>
<td>Hutton, R et al.</td>
<td>2015</td>
<td>Unknown</td>
<td>67</td>
<td>Solitary</td>
<td>Bone, liver</td>
<td>Unknown</td>
<td>3 days</td>
</tr>
<tr>
<td>De Placido, S et al.</td>
<td>2014</td>
<td>4+4</td>
<td>70</td>
<td>Multiple</td>
<td>Bone, lung</td>
<td>Whole-brain radiation (30 Gy) and cabazitaxel</td>
<td>10 months</td>
</tr>
<tr>
<td></td>
<td>2014</td>
<td>4+4</td>
<td>70</td>
<td>Multiple</td>
<td>Bone, lung</td>
<td>Whole-brain radiation and cabazitaxel</td>
<td>16 months</td>
</tr>
<tr>
<td></td>
<td>2014</td>
<td>5+3</td>
<td>72</td>
<td>Multiple</td>
<td>Bone, liver</td>
<td>Whole-brain radiation and cabazitaxel</td>
<td>Unknown</td>
</tr>
<tr>
<td>Cante, D et al.</td>
<td>2013</td>
<td>4+5</td>
<td>70</td>
<td>Multiple</td>
<td>Bone, lymph node</td>
<td>Docetaxel and prednisone for 3 cycles and whole-brain radiation (30 Gy)</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Mitchell, RA et al.</td>
<td>2011</td>
<td>10</td>
<td>72</td>
<td>Multiple</td>
<td>Lung</td>
<td>Craniotomy, excision of tumor, localized radiation therapy (36 Gy), and docetaxel</td>
<td>Unknown</td>
</tr>
<tr>
<td>Izumi, K et al.</td>
<td>2010</td>
<td>Unknown</td>
<td>75</td>
<td>Multiple</td>
<td>Bone, lymph node</td>
<td>Whole-brain radiation and docetaxel</td>
<td>Unknown</td>
</tr>
<tr>
<td>Dewan, S et al.</td>
<td>2009</td>
<td>Unknown</td>
<td>72</td>
<td>Solitary</td>
<td>Unknown</td>
<td>Craniotomy for tumor resection</td>
<td>Unknown</td>
</tr>
<tr>
<td>Cheng, YK et al.</td>
<td>2009</td>
<td>Unknown</td>
<td>72</td>
<td>Multiple</td>
<td>Bone, lymph node</td>
<td>Craniectomy</td>
<td>4 months</td>
</tr>
<tr>
<td>Castro Gomez, JE et al.</td>
<td>2009</td>
<td>3+4</td>
<td>55</td>
<td>Solitary</td>
<td>Bone</td>
<td>Craniotomy, phenytoin, intravenous dexamethasone, and palliative cranial radiotherapy</td>
<td>6 months</td>
</tr>
<tr>
<td>Kim, SH et al.</td>
<td>2008</td>
<td>3+3</td>
<td>79</td>
<td>Solitary</td>
<td>Bone</td>
<td>Gamma knife</td>
<td>6 months</td>
</tr>
<tr>
<td></td>
<td>2008</td>
<td>4+3</td>
<td>72</td>
<td>Multiple</td>
<td>Bone</td>
<td>Whole-brain radiation</td>
<td>7 months</td>
</tr>
<tr>
<td></td>
<td>2008</td>
<td>3+2</td>
<td>77</td>
<td>Solitary</td>
<td>Bone</td>
<td>Gamma knife</td>
<td>7 months</td>
</tr>
<tr>
<td>Cone, LA et al.</td>
<td>2006</td>
<td>4+4</td>
<td>76</td>
<td>Multiple</td>
<td>Lymph nodes, liver</td>
<td>High-dose dexamethasone and whole-brain radiation</td>
<td>4 days</td>
</tr>
<tr>
<td>Inamasu, J et al.</td>
<td>2004</td>
<td>Unknown</td>
<td>77</td>
<td>Solitary</td>
<td>Bone</td>
<td>None</td>
<td>3 weeks</td>
</tr>
<tr>
<td>Chiang, PH et al.</td>
<td>2004</td>
<td>Unknown</td>
<td>61</td>
<td>Solitary</td>
<td>Bone, lung</td>
<td>Craniotomy and complete resection of the tumor</td>
<td>3 weeks</td>
</tr>
<tr>
<td></td>
<td>2004</td>
<td>Unknown</td>
<td>62</td>
<td>Solitary</td>
<td>Bone</td>
<td>Resection of the brain tumor</td>
<td>Alive at 21 months</td>
</tr>
<tr>
<td>Ars, C et al.</td>
<td>2004</td>
<td>Unknown</td>
<td>73</td>
<td>Solitary</td>
<td>Bone</td>
<td>Whole-brain radiation</td>
<td>2 months</td>
</tr>
<tr>
<td>Bentley, AM et al.</td>
<td>2003</td>
<td>3+4</td>
<td>57</td>
<td>Multiple</td>
<td>Bone</td>
<td>High-dose steroids and palliative whole-brain radiotherapy (20 Gy)</td>
<td>4 months</td>
</tr>
<tr>
<td>Neelapu, S et al.</td>
<td>2002</td>
<td>8</td>
<td>66</td>
<td>Multiple</td>
<td>Bone</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Erasmus, CE et al.</td>
<td>2002</td>
<td>5+5</td>
<td>70</td>
<td>Solitary</td>
<td>Lymph nodes, bone, liver and lung</td>
<td>Subtotal resection of the partly cystic tumor and radiation therapy</td>
<td>4 months</td>
</tr>
<tr>
<td>Tsai, V et al.</td>
<td>2001</td>
<td>Unknown</td>
<td>70</td>
<td>Solitary</td>
<td>Bone</td>
<td>Suboccipital craniectomy</td>
<td>Alive at 1 month</td>
</tr>
</tbody>
</table>
considered when CRPC patients complain of symptoms that might result from increased intracranial pressure. In the present case, the time from the diagnosis of prostate cancer to the detection of brain metastases was 36 months, which is consistent with previous reports. Our patient did not experience delirium, and the first symptom was severe headache that could not be controlled by analgesics. We considered the possibility of brain metastases and then proceeded to detect them. Our treatment for brain metastases was considered to be temporarily successful. According to previous reports, for solitary metastasis, surgery is an option. Our patient had multiple metastases, and, consequently, whole-brain radiation was the chosen treatment. Although we did not evaluate the brain metastatic lesions after treatment, the patient’s level of consciousness and general condition had clearly improved.

**Imaging modality for accurate diagnosis of metastatic brain cancer**

MRI is considered the most sensitive imaging modality for metastatic brain tumors. Furthermore, Gd contrast-enhanced MRI is important for accurate diagnosis of the number and locations of brain metastases. In general, non-hemorrhagic lesions of brain metastases are hypointense compared with normal brain on non-contrast-enhanced T1WI. The signal intensity of hemorrhage from metastatic tumor on T1-weighted contrast-enhanced MRI images varies over time. On T2WI, metastatic tumors often present as hypointense regions, and fluid-attenuated inversion recovery can reveal peritumoral vasogenic edema. On contrast-enhanced MRI, most metastatic brain tumors are enhanced, with enhancement patterns being solid, rimmed, or mixed. On contrast-enhanced CT can be used to detect life-threatening sequelae of metastatic tumors, such as hemorrhage, hydrocephalus, and herniation. Contrast-enhanced CT can reveal the border lines of enhanced tumors. However, CT, with or without contrast-enhancement agents, has limited use for an accurate diagnosis because of low soft tissue resolution. In a study investigating what additional information could be gained by contrast-enhanced MRI in patients with solitary brain metastasis according to diagnostic contrast-enhanced CT, Schellinger et al. confirmed that there were multiple metastases in 31% of cases. Metastatic lesions that could not be detected with contrast-enhanced CT were on average 2 cm smaller than those identified using both modalities. Schellinger et al. concluded that MRI was indeed superior to contrast-enhanced CT in the diagnosis of brain metastases.

In the present case, non-contrast-enhanced brain CT did not reveal metastatic tumors, but it was employed to exclude life-threatening disorders such as cerebral hemorrhage. However, to investigate the cause of the patient’s severe headache, we performed brain Gd contrast-enhanced MRI (Fig. 2B, C), and this imaging modality successfully revealed the tumors. Non-contrast-enhanced MRI can detect large metastatic tumors, but Gd contrast-enhanced MRI should be used for accurate diagnosis of metastatic brain tumors because knowledge of the number and characteristics of tumors is necessary for choosing the appropriate therapy.

**Efficacy of cabazitaxel and radiation therapy for brain metastases of prostate cancer**

The present patient was treated with cabazitaxel after the PSA level again became elevated after 3 cycles of docetaxel treatment and sequential use of enzalutamide and abiraterone. Cabazitaxel is believed to easily cross the BBB. Nonlinear accumulation of cabazitaxel in the brains of rats was observed by saturation of the P-glycoprotein in the BBB. However, in clinical practice, the efficacy of cabazitaxel for brain metastases is still unproven because of the rarity of brain metastases of prostate cancer. Three patients who were treated with cabazitaxel for brain metastases of prostate cancer have been reported. In all three cases, brain metastases were detected by MRI before starting cabazitaxel. Whole-brain radiotherapy at a dose of 30 Gy was administered in all three cases. Two cases showed partial remission with the brain metastases reduced by half (PSA reduction rate: 60%). One case showed complete remission with the brain metastasis undetectable by MRI (PSA reduction rate: 90%).

In the present case, the symptoms elicited by brain metastases occurred after the fourth cycle of cabazitaxel. To our knowledge, there have been no reports of brain metastases occurring during cabazitaxel therapy. Although PSA levels were maintained at relatively low levels in the present case, brain metastases still occurred. Consequently, we believe that cabazitaxel with radiation therapy may be necessary to treat brain metastases. The efficacy of whole-brain radiotherapy is limited. However, the combination of cabazitaxel and radiation therapy for brain metastases of CRPC has the potential to elicit a good response. To accumulate cases of brain metastases, the effectiveness of cabazitaxel and radiation therapy for brain metastases of CRPC should be reported in detail.

**Conclusions**

We have described a patient in whom multiple brain metastases were diagnosed during cabazitaxel therapy for CRPC. The possibility of brain metastases should be investigated using Gd contrast-enhanced MRI when CRPC patients complain of symptoms that may be attributable to increased intracranial pressure during cabazitaxel therapy.
Conflicts of Interest
The authors have no conflicts of interest to report.

References


12. Inamasu J, Nakamura Y, Saito R, Kuroshima Y, Mayanagi K, Orii M, Ichikizaki K: Cerebellar hemorrhage secondary to cranial me-