CLINICAL STUDY – PATIENT STUDY

Central nervous system metastases from castration-resistant prostate cancer in the docetaxel era

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Abstract Central nervous system (brain or leptomeningeal) metastases (BLm) are considered rare in castration-resistant prostate cancer (CRPC) patients. Now that docetaxel has become the reference drug for first-line treatment of CRPC, patients whose disease is not controlled by hormonal manipulations may live much longer than before and have higher risk of developing BLm. We retrospectively reviewed the records of all patients with CRPC attending our centres from 2002 to 2010, and identified all of those who were diagnosed as having BLm and received (or were considered to have been eligible to receive) docetaxel-based treatment. We identified 31 cases of BLm (22 brain metastases and 9 leptomeningeal metastases) with an incidence of 3.3%. BLm-free survival was 43.5 months, and survival after BLm discovery was 4 months. With six patients surviving for more than 1 year after developing BLm, the projected 1-year BL-S rate was 25.8%. The findings of our study may be relevant in clinical practice as they indicate that incidence of BLm in CRPC patients in the docetaxel era seems to be higher than in historical reports, meaning that special attention should be paid to the appearance of neurological symptoms in long-term CRPC survivors because they may be related to BLm.

Keywords Castration-resistant prostate cancer · Brain metastases · Leptomeningeal metastases · Docetaxel · Chemotherapy

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Introduction

Prostate cancer is the most frequent cancer developed by men, with annual incidence of 217,000 new cases in the USA and 382,000 new cases in Europe, and mortality rates of 32,000 and 90,000 per year, respectively [1, 2]. Prostate cancer is highly responsive to anti-hormonal therapy, and can be controlled for several years by means of androgen deprivation even in the presence of metastases; however, even responding patients eventually become resistant and have shortened life expectancy.

Until 2004, oncologists had few options for treatment of castration-resistant prostate cancer (CRPC). Mitoxantrone was the only active and approved drug, but its only significant effect was symptom relief and it did not increase survival [3, 4]; consequently, patients with CRPC were expected to live for no more than 8–10 months [5].

This changed in 2004, when two large phase III trials showed that the anti-microtubule agent docetaxel significantly prolonged median overall survival to 17–19 months [6, 7]. Furthermore, because of its increasingly wider use in clinical practice and the lack of a true second-line chemotherapy, it is possible that patients who have responded to first-line docetaxel may be re-treated with it several times before the appearance of real docetaxel resistance, with median survival time of almost 30 months [8, 9]. Now that docetaxel has become the reference drug for first-line treatment of CRPC, patients whose disease is not controlled by hormonal manipulations may live much longer than 1 year. As has been observed in the case of long-term survivors with colorectal cancer [10] or breast cancer [11], this increased life expectancy is likely to lead to changes in the profile of CRPC, including more frequent occurrence of brain metastases [12].

Central nervous system (brain or leptomeningeal) metastases (BLm) are considered rare in CRPC patients. With the exception of a limited number of case reports, they have only been described in two large, single-centre retrospective surveys [13, 14]. These were not specific for CRPC, covered a long time period and, as they were published before 2004, could not reflect any effect of docetaxel on the incidence of BLm.

The aim of this retrospective multicentre study is to assess the incidence and characteristics of BLm in CRPC patients after the introduction of docetaxel into clinical practice.

Materials and methods

Patients

We retrospectively reviewed the records of all patients with CRPC attending our centres from 2002 to 2010, and identified all of those who were diagnosed as having BLm and received (or were considered to have been eligible to receive) docetaxel-based treatment. The drug was approved for CRPC in 2004, but the analysis was started in 2002 as some patients received docetaxel in the context of clinical trials. All of the patients included in the analysis had to have at least one radiologically proven diagnosis of brain or leptomeningeal metastasis based on brain computed tomography (CT) with contrast medium or brain magnetic resonance imaging (MRI); they also had to have undergone complete restaging based on chest and abdomen CT in order to exclude the presence of a second tumour capable of producing central metastases. All patients with a previous diagnosis of a second tumour were excluded. The other exclusion criteria were the presence of a simple dural lesion from a contiguous cranial or vertebral metastasis and the absence of concomitant parenchymal lesions.

Statistical methods

Patient demographics, disease characteristics, treatments and outcomes are presented using descriptive statistics. The incidence of central metastases from CRPC was estimated by dividing the number of patients with BLm by the total of all of the patients at risk during the observation period.

Time-to-event variables are summarised by median values (Kaplan–Meier method) and 95% confidence intervals (CI). BLm-free survival (BL-FS) was defined as the number of months from date of diagnosis of the primary tumour to date of BLm detection. BLm survival (BL-S) was defined as the number of months between date of BLm detection and date of death or last follow-up examination. Survival was analysed using the Statistical Package for Social Sciences software, version 11.0 (SPSS Inc., Chicago, IL).

Results

Our review of a consecutive series of 943 cases of CRPC treated in nine Italian hospitals between 2002 and 2010 identified 31 cases of BLm (incidence 3.3%). Seventy-three patients were not considered eligible to receive docetaxel because of old age or poor performance status. No patient was excluded from the analysis due to previous diagnosis of another cancer. Table 1 shows the main characteristics of the patients and their prostate cancer history. Twenty-two had brain metastases (12 developed a single metastasis) and nine had leptomeningeal metastases. Median BL-FS was 43.5 months (range 6–173 months); metastases were spread out very widely over time with a continuous distribution along the range. Twenty-two percent, 11% and 52% of patients developed BLm within the first, second and fifth year after diagnosis of metastatic

Table 1 Patient characteristics

No. of patients	31
Age	
Median	62 years
Range	51–78 years
Gleason score	
Median	8
Range	7–10
Histotype	
Adenocarcinoma	31
History of treatments for prostate cancer	
Local treatment	
Surgery	8
Radiotherapy	7
None	16
Hormonal treatments	
≤ 2	27
>2	4
Chemotherapy courses[a]	
0	5
1	12
>1	12
Unknown	2
Interval between prostate cancer diagnosis and CRPC development	
Median	23 months
Range	7–141 months

[a] Rechallenges with docetaxel were considered separate courses

Table 2 BLm characteristics

	Brain metastases	Leptomeningeal metastases
No. of cases	22	9
No. of metastases		
Median	1	NA
Range	1–8	NA
Neurological symptoms		
Yes	17	8
No	5	1
Diagnosis		
CT	6	3
MRI	16	6
Local treatment		
Surgery + WBI	5	0
Surgery	1	0
WBI	7	2
γknife	1	0
None	8	7
Chemotherapy after BLm		
Yes	10	1
No	12	8

WBI whole-brain irradiation, *NA* not applicable

Fig. 1 Survival after BLm development

disease, respectively, while 15% of cases occurred after the 5th year. In all cases, central nervous system (CNS) was not the first metastatic site and BLm occurred after the appearance of other typical metastases (skeletal and/or lymph nodal). The BLm were discovered during docetaxel-based chemotherapy in 7 cases, after docetaxel-based chemotherapy in 16 cases, and before any docetaxel-based chemotherapy in 8 cases. CNS radiological tests were not routinely prescribed during follow-up, even for clinical trials, so the BLm diagnosis was made by CT scan or MRI after occurrence of central symptoms. The most frequently reported symptoms were headache (35% of the patients), confusion (10%), coma (10%) and hyposthenia (10%).

Table 2 presents the characteristics of the BLm and their treatments. Fourteen patients (64%) with brain metastases received a local treatment, compared with two patients with leptomeningeal metastases (28%). After BLm diagnosis, 11 patients received further chemotherapy (docetaxel in 9 cases, mitoxantrone in 2). Six patients survived for more than 1 year after developing BLm; five of these long-term survivors had brain metastases and one had leptomeningeal metastases; three underwent surgery, two rece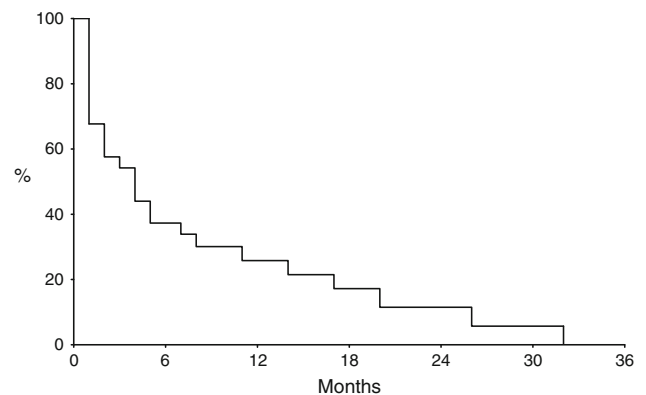ived radiotherapy, and one was treated with docetaxel. To date all but two patients are dead; the cause of death was mainly related to BLm occurrence, except for five long-term survivors who died due to non-CNS progressive disease. Median BL-S was 4 months (95% CI 1–7 months) for the whole group, while it was 1 and 4 months for patients with leptomeningeal and brain metastases, respectively. The projected 1-year BL-S rate was 25.8% (Fig. 1).

Discussion

To the best of our knowledge, this is the first study of BLm in patients with CRPC in the docetaxel era. We

retrospectively reviewed 943 metastatic CRPC patients treated between 2002 and 2010, all of whom were treated with or eligible for docetaxel-based chemotherapy. Thirty-two patients had BLm, nine of whom had leptomeningeal metastases.

Development of BLm in prostate cancer patients may be due to one of two mechanisms: the first is a direct extension of skull metastases, which is responsible for the development of dural lesions; the second mechanism is hematogenous spread from pre-existing metastatic sites through lymphatic vessels, which can cause leptomeningeal and intraparenchymal lesions. In particular, spread through the paravertebral venous plexus bypasses bone and other sites [14, 15].

Whatever the mechanism, occurrence of BLm is usually considered rare. Most of the data concerning the incidence of brain metastases come from occasional reports or large autopsy series because they were usually asymptomatic in living patients and discovered only incidentally after death [13]. The first retrospective study was published in 1976 by Catane et al., who found an incidence of 4.4% in 91 patients with prostate carcinoma [16]; in 1984, Taylor et al. reported that intracranial metastases had been found in 14 out of 126 autopsies (11.1%) performed between 1954 and 1981 [17].

However, this high incidence was not confirmed by two large studies carried out by the MD Anderson Cancer Institute. The first was published in 1999 by McCutcheon et al. [13], who reviewed 7,994 patients with prostate cancer treated over an 18-year period and found 38 cases of brain metastases (an incidence of 0.7%). Median time from diagnosis of prostate carcinoma to discovery of brain metastases was 28 months, and median overall survival was 9.2 months. The second study, which was published in 2003 [14], considered 16,280 patients with pre or post mortem diagnosis of prostate carcinoma between 1944 and 1998, and found 131 who developed craniospinal metastases (53 radiological and 78 autopsy diagnoses); as 103 of these had parenchymal metastases and 5 had leptomeningeal disease, the incidence of true brain metastases was 0.63%. Median time from first tumour diagnosis was 35 months in the patients with adenocarcinoma and 48 months in those with small cell carcinoma.

All these reports were published before the introduction of docetaxel for treatment of prostate cancer, and rarely included patients treated with chemotherapy. Only the study by McCutcheon et al. identified 18/38 patients (47.3%) who had received chemotherapy for 64.2% of transitional and small cell carcinomas and 37.5% of adenocarcinomas.

In our series, the incidence of patients with BLm (all from prostate adenocarcinomas) was 3.3%, which is higher than either of the rates indicated by the MD Anderson Cancer Center studies, and the median time from diagnosis of prostate carcinoma to appearance of brain metastases was longer: 43.5 months (6–173 months) versus 28–35 months.

One possible explanation for these findings is the introduction of docetaxel, which is usually administered as first-line treatment to all patients with CRPC and no contraindications, because it prolongs overall survival; pivotal trials extended median survival to 17–19 months [6, 7], which is longer compared with the less than 12 months survival expected in the 1990s for CRPC patients [5]. Our data confirmed this finding, since the median survival of our overall group of 943 patients was 22 months. By modifying the natural history of the disease, it may give the tumour enough time to develop BLm [18, 19]. This hypothesis has also been proposed when the adoption of new therapeutic strategies in other oncological contexts has increased the rate of long-term survivors and, therefore, the risk of developing CNS metastases [10, 11, 20].

Furthermore, the inability of docetaxel to penetrate the blood–brain barrier may limit its brain concentrations [21] and thus reduce the possibility of eradicating tumour cells from the CNS [22]. Development of resistance to docetaxel mainly depends on its high substrate affinity for multidrug resistance proteins, particularly the adenosine triphosphate (ATP)-dependent drug efflux pump P-glycoprotein (P-gp, known as ABCB1), because tumour cells expressing P-gp can be responsible for both constitutive and acquired docetaxel resistance [23]. It is worth noting that ABCB1 is expressed by endothelial cells of the blood–brain barrier [24] and can limit exposure of nervous tissue to substrate drugs by actively transporting them from nerves into the systemic circulation [25].

Given the higher incidence of BLm due to the prolonged survival of CRPC patients and the inability of docetaxel to penetrate the blood–brain barrier, it is interesting to note that cabazitaxel, a new taxane active after docetaxel failure [26], can reach high concentrations in brain tissues [27].

Our study has two limitations. First of all, we retrospectively evaluated a smaller series of patients than the historical series. Secondly, we have no data concerning the incidence of BLm in our centres before docetaxel was introduced into clinical practice, and so we cannot compare our results with those of the pre-docetaxel era. Furthermore, as patients with CRPC were rarely referred to medical oncologists before the use of chemotherapy, it is possible that the incidence of BLm was underestimated in the past. On the other hand, our series was specifically devoted to evaluate only BLm, excluding those metastases that could be simply considered an epiphenomenon of cranial bone metastases with a quite different development mechanism.

Moreover, the historical series were not specifically devoted to CRPC and the screened populations were quite

different from the present one. For example, McCutcheon et al. evaluated a group of 7,994 patients with either hormone-sensitive disease or CRPC [13]. In the series of 16,280 patients from Tremont-Lukats et al., 6,282 patients developed or presented metastatic disease [14]; if we consider the metastatic condition as closer to (but not exactly overlapping with) CRPC and we use 6,282 as a denominator, the incidence of brain metastases would be 1.6%, which is anyway half of the 3.3% incidence observed in the present study. In this view, it clear that different conditions produced different denominators and the present series could not be exactly matched to the historical ones.

Despite the above limitations, the findings of our study may be relevant in clinical practice as they indicate that incidence of BLm in CRPC patients in the docetaxel era seems to be higher than in historical reports, which means that special attention should be paid to appearance of neurological symptoms in long-term CRPC survivors because they may be related to BLm. They may be a result of changes in the survival of CRPC patients induced by the introduction of docetaxel into clinical practice, which has enabled control of systemic disease but cannot prevent dissemination of cancer cells into the CNS. This possibility suggests that further studies of larger patient series are warranted in the attempt to assess the incidence of BLm in CRPC as well as the effectiveness and cost-effectiveness of CNS screening for early detection of BLm.

Conflict of interest The authors declare that they have no conflict of interest.

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