Clin. Exp. Metastasis, 1994, **12**, 226–230

Central nervous system as sanctuary site of relapse in patients treated with chemotherapy for metastatic testicular cancer

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(Received 21 January 1994; accepted in revised form 21 February 1994)

Isolated central nervous system relapse in patients treated successfully with cisplatin-based chemotherapy for testicular cancer has been described infrequently. In a retrospective analysis we identified this complication in six of 417 patients. Five of the six patients had advanced pulmonary dissemination at onset of chemotherapy, and post-chemotherapy surgery did not reveal viable tumour tissue in any of these cases. All six patients developed a single cerebral metastasis during complete remission a median four months after discontinuation of chemotherapy. Five patients were treated with surgery and subsequent radiotherapy, one patient with irradiation alone. Three patients are alive relapse-free 19, 62 and 86 months after diagnosis of cerebral relapse. One patient was alive with cerebral disease for 12 months without evidence of systemic recurrence. Our data demonstrate that the brain may act as a sanctuary site in chemotherapy-treated testicular cancer. A review of the literature shows that an isolated cerebral relapse is an extremely rare complication, but carries a relatively favourable prognosis.

Keywords: cerebral metastasis, chemotherapy, sanctuary site, testicular cancer

Introduction

The introduction of cisplatin by Einhorn and Donohue in 1977 [1] has considerably improved the clinical outcome of patients with metastatic germ cell tumours. However, prognosis remains relatively poor for patients with a large tumour burden and specific sites of metastatic disease. In three recently published studies the presence of brain metastases prior to introduction of chemotherapy has been recognized as an adverse prognostic factor [2–4]. Moreover, patients who develop cerebral metastases in association with a systemic relapse after chemotherapy carry a very poor prognosis [5–7].

A relapse after chemotherapy confined to the brain has been reported infrequently. However, sparse data in the literature suggest that this patient group has a considerably better clinical outlook than patients with cerebral metastases at the time of diagnosis or patients relapsing in the brain and systemically [6, 8]. This report summarizes our experience with isolated central nervous system (CNS) relapses occurring in patients who were successfully treated with chemotherapy. Among 417 male patients with metastatic germ cell tumours treated with cisplatin-based chemotherapy in curative intention from 1979 to 1992, this clinical phenomenon has been observed in six cases, accounting for an incidence of 1.4%.

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Case reports

Case 1

A 27-year-old man presented with a left testicular mass. Embryonal carcinoma was diagnosed at orchiectomy. Retroperitoneal lymphadenectomy revealed no nodal involvement, and chest X-ray was normal. Nine months later the patient presented with chest pain, and a repeat chest X-ray disclosed multiple pulmonary metastases. Serum alpha-fetoprotein was slightly elevated at 28 ng/ml (normal < 15 ng/ml), while human chorionic gonadotropin was within a normal range. The patient was treated with five cycles of chemotherapy consisting of cisplatin, vinblastine and bleomycin as described elsewhere [1]. Serum alpha-fetoprotein normalized after the first treatment course. Thoracotomy was performed to resect post-chemotherapy tumour residuals, and histologic examination did not reveal any viable tumour tissue. Four months later the patient developed a weakness of his right arm, and CT brain scan disclosed a large left parietal lobe lesion. Serum tumour markers were within normal limits. The mass was resected and histologic examination confirmed embryonal carcinoma. The patient was treated with 45 Gy of whole brain irradiation. The weakness of the right arm partially resolved, and 7 years later there is only a minor neurologic impairment. The patient is fully employed as a computer specialist. Eight years after diagnosis of the left testicular tumour he developed a seminoma of his right testicle. After orchiectomy he was given 26 Gy of retroperitoneal radiation. Presently, there is no evidence of recurrent disease.

Case 2

A 26-year-old man presented with swelling of the left testis. Orchiectomy revealed a diagnosis of pure seminoma, but tumour marker analysis indicated the presence of non-seminomatous elements (alpha-fetoprotein 195 ng/ml, human chorionic gonadotropin 29 430 U/l). Abdominal and thoracic CT scan disclosed an extensive retroperitoneal lymph-node involvement and multiple pulmonary metastases. The patient was treated with one cycle of chemotherapy consisting of vinblastine, ifosfamide and cisplatin [9] and a further four courses consisting of etoposide, cisplatin, bleomycin and cyclophosphamide [10]. After chemotherapy serum tumour markers were within normal limits. The patient underwent thoracotomy and retroperitoneal lymph-node dissection. Histologic examination of tumour residuals did not reveal any viable tumour tissue. Three months later the patient developed headache and an impaired coordination of his right arm. CT brain scan revealed a left occipital lobe lesion. Serum alpha-fetoprotein and human chorionic gonadotropin were elevated at 82 ng/ml and 137 U/l, respectively. Craniotomy was performed, and histologic examination of the removed metastasis disclosed teratocarcinoma. Postoperatively serum tumour markers normalized. The patient was treated with 40 Gy of whole brain irradiation, and additional radiation (20 Gy) was delivered to the focus. The neurologic impairment resolved apart from a minute homonymous hemianopia. Five years later the patient is free of relapse, and he is fully employed as a soldier.

Case 3

A 33-year-old man presented with a right testicular mass. Orchiectomy revealed embryonal carcinoma. Abdominal and thoracic CT scan disclosed a large retroperitoneal mass and multiple pulmonary metastases. A CT brain scan did not reveal any abnormalities. Serum alpha-fetoprotein and human chorionic gonadotropin were elevated at 645 ng/ml and 246 U/l, respectively. The patient was treated with four cycles of an intensified chemotherapy regimen consisting of cisplatin, etoposide and ifosfamide [11]. Serum tumour markers normalized, and post-chemotherapy retroperitoneal lymph-node dissection did not reveal any viable tumour. A small pulmonary residual resolved spontaneously. Four months after discontinuation of chemotherapy the patient developed left-sided hemiparesis. CT brain scan disclosed a large right parietal lobe lesion. Serum tumour markers did not rise. The cerebral metastasis was excised, and postoperatively 50 Gy of whole brain irradiation was administered. There was only a minor regression of neurologic deficits, and the patient is not able to return to work. Nineteen months after diagnosis of cerebral relapse there is no evidence of recurrent disease.

Case 4

A 27-year-old man presented with a right testicular mass and a considerable weight loss. Orchiectomy revealed a mixed germ-cell tumour consisting of seminoma, choriocarcinoma and yolk sac tumour. Abdominal and thoracic CT scan showed an extended retroperitoneal and mediastinal lymph-node involvement. CT brain scan was normal. Serum tumour markers, human chorionic gonadotropin and alpha-fetoprotein were elevated at 83 000 U/l and 2376 ng/ml, respectively. Five cycles

of chemotherapy consisting of etoposide, cisplatin, bleomycin and cyclophosphamide [10] were administered, and physical examination, tumour marker analysis and a repeat CT scan documented a complete remission. Three months later the patient returned to work. A follow-up examination 7 months after discontinuation of chemotherapy, which included physical status, abdominal and thoracic CT scan and serum tumour markers, yielded normal results. Two months later the patient experienced a left-sided weakness and focal seizures. CT brain scan disclosed a right parietal lobe lesion, and serum human chorionic gonadotropin was elevated at 177 U/l. The cerebral metastasis was excised, and postoperatively whole brain irradiation was initiated. After administration of a dosage of 20 Gy the patient developed pancytopenia and died from candida pneumonia. The cause of pancytopenia remained obscure. Five days prior to the patient's death serum human chorionic gonadotropin was within normal limits, and there was no clinical evidence of tumour recurrence.

Case 5

A 65-year-old man presented with a left testicular swelling. Orchiectomy was performed and histologic examination revealed embryonal carcinoma. Serum tumour markers were not elevated at any time. Retroperitoneal lymph-node dissection showed no nodal involvement, and chest X-ray was normal. Eleven months later the patient presented with large pulmonary metastases. He was treated with four cycles of chemotherapy consisting of etoposide, cisplatin, bleomycin and cyclophosphamide [10], and post-chemotherapy thoracotomy showed no viable tumour. Two months later the patient presented with left homonymous hemianopia and left hemiparesis. CT brain scan showed a right occipital lobe lesion with haemorrhage and a considerable mass effect. The cerebral metastasis was excised, and postoperatively neurologic impairment improved markedly. Whole brain irradiation was initiated, but the patient developed new neurologic deficits, and a repeat CT brain scan revealed a new right occipital lobe lesion. The patient deteriorated rapidly and died 5 weeks after diagnosis of cerebral metastasis.

Case 6

A 26-year-old man presented with right testicular swelling. At orchiectomy embryonal carcinoma was diagnosed. Serum tumour markers, alpha-fetoprotein and human chorionic gonadotropin were elevated at 200 ng/ml and 150 U/l, respectively, and normalized after orchiectomy. Retroperitoneal lymph-node dissection revealed no involvement. Three months later the patient presented with multiple pulmonary metastases, and serum human chorionic gonadotropin was slightly elevated at 27 U/l. The patient was treated with four cycles of chemotherapy consisting of cisplatin, vinblastine and bleomycin [1]. Serum tumour markers were within normal limits after the first treatment course. At post-chemotherapy thoracotomy no viable tumour was identified. Six months later the patient developed convulsions. CT brain scan disclosed a left parietal lobe lesion. Human chorionic gonadotropin was slightly elevated at 7.1 U/l (normal < 5 U/l). Surgical excision was taken into consideration but was not performed, as the lesion was located near the motor cortex. Whole brain irradiation (50 Gy) was administered, and a repeat CT scan did not show any abnormality. However, the patient still suffered from seizures. During the following months he developed progressive neurologic deficits, and a repeat CT brain scan disclosed an increasing lesion at the initially involved region. Serum tumour markers, human chorionic gonadotropin and alpha-fetoprotein rose to 27 U/l and 39 ng/ml, respectively. The patient died from brain oedema 12 months after diagnosis of cerebral relapse. There was no evidence of recurrent disease at other sites.

Discussion

Prior to the introduction of cisplatin-based chemotherapy, approximately 40% of patients with non-seminomatous testicular cancer who died with progressive disease were found to have brain metastases at autopsy [12]. Whereas in an early report by Williams and Einhorn cerebral metastases were clinically manifest in 15% of patients with disseminated germ-cell tumours [13], this rate decreased to 2–4% in recently published studies [6]. Brain metastases predominantly develop in patients with non-seminomatous germ-cell tumours; they are extremely rare in patients with pure seminomas [7, 14]. The majority of patients with cerebral metastases have concomitant or preceding extended pulmonary dissemination (five cases in our series); few cases of CNS relapse have been reported in patients with prior disease confined to the lymph nodes [6, 14] as in the above-described case 4.

Whereas cerebral metastases at presentation are described in almost all large series of chemo-

therapy-treated testicular cancer, only 16 cases of isolated CNS relapse have been documented in the English language literature [6, 8, 14–17]. An additional six cases have been described in this paper. Out of these 22 patients, 21 presented with a single cerebral metastasis; multiple cerebral lesions were identified only in one patient. In our series CNS relapse became clinically manifest 2–9 months (median 4 months) after discontinuation of primary treatment. All six patients had attained no evidence of disease status as documented by clinical and radiographic examinations and tumour marker analysis. Five patients had undergone post-chemotherapy surgery, and in all cases histologic examination did not show viable tumour tissue. The development of sole cerebral metastasis during complete remission of chemotherapy-treated testicular cancer demonstrates that the CNS may be a sanctuary site for malignant cells in germ-cell tumours. This view is supported by the fact that three patients in our series are long-term survivors after CNS relapse has been locally controlled by surgery and subsequent radiotherapy. A further patient was alive with cerebral disease for 12 months without showing evidence of systemic relapse.

A relative weakness of this study is that CT brain scans were not performed routinely prior to onset of chemotherapy. However, no patient in our series initially showed any clinical sign of CNS involvement. Two patients, who were treated in clinical trials, underwent CT brain scans as part of initial staging procedures; these examinations did not reveal any abnormalities. It cannot be excluded that the other four patients had asymptomatic cerebral lesions prior to the start of chemotherapy.

At present, no consensus has been reached with regard to the most effective treatment of brain metastases in patients with germ-cell tumours. Chemotherapy plays an important role in the management of initially presenting cerebral disease and can lead to complete remissions without incorporating other treatment modalities [18]. However, the role of chemotherapy is defined less precisely for cases presenting with an isolated CNS relapse. Whereas Spears *et al.* favoured a combined modality approach consisting of surgery, irradiation and chemotherapy [6], we did not use chemotherapy in this patient group. Raina *et al.* also did not treat their patients with chemotherapy [14]. In contrast, Logothetis *et al.* used concurrent irradiation and chemotherapy [8]. Cisplatin, the most active agent against testicular cancer, poorly penetrates the blood–brain barrier [19]. In cases of clinically manifest cerebral disease cisplatin may reach the brain in higher concentrations which could explain the successful treatment of cerebral metastases with chemotherapy alone [18]. Etoposide and bleomycin also have been found to reach the brain in patients with cerebral tumours [19, 20].

The role of surgery in the treatment of brain metastases of germ-cell tumours also is discussed controversially. Some authors favour surgical excision of a single cerebral metastasis, as it can lead to rapid recovery of neurologic impairment and it can prevent the risk of haemorrhage [21]. Recently, a randomized study was published which compared surgery and radiotherapy versus radiotherapy alone in the treatment of single cerebral metastasis of solid tumours [22]. This study showed a superiority for the combined approach; but conclusions have to be drawn with caution, since this study did not include patients with testicular cancer. Nevertheless, a combined approach of surgery and subsequent irradiation was successful in three of five patients in our series.

Whereas prognosis is extremely poor for patients presenting with relapse in the CNS and other systemic sites, a relapse after chemotherapy confined to the brain carries a much better prognosis. Considering our patients and the cases described in the literature, 14 out of 22 patients (64%) were alive without evidence of relapse at the time of the reports.

In conclusion, isolated CNS relapse is a rare complication in chemotherapy-treated testicular cancer. The majority of patients present with a single metastasis a few months after the end of chemotherapy. Surgery and subsequent radiotherapy can lead to relapse-free long-term survival, but larger numbers of patients are necessary to define the most effective treatment precisely. Prognosis is favourable in contrast to patients relapsing in the brain and systemically.

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