Leptomeningeal carcinomatosis in relapsed non-seminoma testis: a 1-year complete remission with high-dose chemotherapy

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A 1-year complete remission could be achieved with high-dose systemic chemotherapy in a 33-year-old patient with relapsed germ cell tumor presenting with leptomeningeal carcinomatosis (LC). Although LC in general has a very poor prognosis for patients with chemosensitive malignancies, systemic chemotherapy should be considered. ***Anti-Cancer Drugs*** **16:897–899 © 2005 Lippincott Williams & Wilkins.**

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Introduction

Although the overall prognosis for patients with metastatic testicular cancer (TC) is generally good, the chances for long-term survival are only moderate in the case of relapse. The prognosis at relapse varies, and can be predicted by primary tumor location, response to first-line treatment, duration of this response and serum levels of the tumor markers at relapse [1]. For relapsed patients, high-dose chemotherapy followed by autologous stem cell rescue is most commonly used. Several phase II trials have indicated a 10% improvement in median overall survival with this strategy, with long-term remissions varying between 15 and 40% depending on risk factors [1–5].

Central nervous system (CNS) involvement is present in about 1% at the time of initial diagnosis and develops in approximately 8% at some time during the course of the disease [6]. In the case of relapse with CNS involvement, prognosis is generally poor, with a 5-year survival rate of below 5%. The optimal treatment for this group of patients has yet to be established [2]. Presentation of relapsed germ cell tumor by frank leptomeningeal carcinomatosis (LC) is very rare and has not been described for non-seminoma [7]. As a consequence, evidence for treatment choice is lacking. The literature on other solid malignancies with LC describes an extremely poor prognosis with a median survival of several months, despite treatment with chemotherapy (either intrathecal or intravenous) or with radiotherapy [8–10].

In this report we present a patient with a relapsed non-seminoma testis presenting with an abundant LC. Upon treatment with high-dose i.v. chemotherapy with autologous stem cell support he achieved a 1-year complete remission. Diagnostic and treatment issues will be discussed.

Case report

A 33-year-old male presented in December 2002 with a left testicular mass. Histology of the orchidectomy revealed a non-seminoma testis (embryonal cell carcinoma with seminoma component). Computed tomography (CT) scanning displayed pathological para-aortal lymph nodes around the left internal iliac artery and several lung metastases. The plasma levels of the tumor markers were elevated: β-human chorionic gonadotropin (β-HCG) 624 ng/ml (normal < 1 ng/ml), α-fetoprotein (AFP) 27 μg/ml (normal < 3 μg/ml) and lactate dehydrogenase (LDH) 617 U/l (normal < 400 U/l). The patient was treated according to the IGCCCG intermediate-risk group with 4 cycles of BEP chemotherapy (bleomycine 30 mg weekly, etoposide 500 mg/m^2/cycle, cisplatin 100 mg/m^2/cycle) [11]. The tumor markers normalized after the second cycle and CT scans in March 2003 showed a complete remission.

In July 2003 the patient developed complaints of headaches and visual disturbances which were paralleled by a rise of β-HCG (52 ng/ml), AFP (15 μg/ml) and LDH (584 U/l). CT scanning of the head revealed a solitary occipital brain metastasis without signs of edema.

Metastasectomy was performed and histological examination confirmed embryonal cell carcinoma. In addition, whole-brain irradiation was applied (20 fractions of 1.8 Gy, with an additional boost of 5×1.8 Gy). The tumor

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markers normalized within several weeks following resection.

In November 2003 the patient developed ischialgic pain in the pelvic area, irradiating to the right leg and worsening upon coughing. The tumor markers in the plasma remained normal. CT scanning demonstrated three pulmonary metastases. Since a frank systemic relapse was diagnosed, the patient was transferred to our hospital for salvage chemotherapy.

An additional work-up was performed. Magnetic resonance imaging (MRI) showed two intrathecal metastases at the level of the first lumbar vertebra (1 and 1.5 cm, respectively) and pathologically thickened nerve radixes lumbosacral. MRI of the cerebrum did not show brain metastasis or signs of increased intracranial pressure or hydrocephalus. A lumbar puncture was performed and a normal opening pressure was measured. Biochemical analysis of the cerebral spinal fluid (CSF) revealed an increased protein level (773 mg/l, normal < 490 mg/l) and a normal glucose level. Cytological examination of the CSF showed a large amount of malignant cells, which were cytomorphologically compatible with the original tumor.

It was concluded that the patient had a systemic relapse of non-seminoma testis with pulmonary metastasis and abundant LC. We estimated the prognosis of this patient to be dismal, which was confirmed by the literature and expert opinions [1]. Nonetheless, we decided to try to achieve disease control by treatment with high-dose chemotherapy. The strongest reason favoring treatment was that germ cell tumors in relapse frequently remain highly chemosensitive. We choose repeated ablative chemotherapy with autologous peripheral stem cell reinfusion according to the phase II study protocol of The Netherlands Working Party on Autologous Transplantation in Solid Tumors [5]. No additional administration of intrathecal chemotherapy was planned.

The first cycle consisted of ifosfamide 4 g/m^2 on day 1 and etoposide 100 mg/m^2 on days 1, 2 and 3 followed by granulocyte colony-stimulating factor (G-CSF) 10 μg/kg. Hematopoietic stem cells were collected at day 9 by hemapheresis, resulting in a harvest of 6.2×10^6 CD34$^+$ cells.

The second cycle could be given at day 21, and consisted of carboplatin 800 mg/m^2 on day 1 and etoposide 500 mg/m^2 on days 1, 3 and 5 followed by G-CSF. This was accompanied by grade 3 thrombocytopenia and neutropenia, and manageable mucositis.

At day 59 the first course of myeloablative CTC chemotherapy was given consisting of carboplatin (1600 mg/m^2 divided over days -6 through -3), thiotepa (480 mg/m^2 divided over days –6 through –3) and cyclophosphamide (6 g/m^2 divided over days –6 through –3). Stem cell reinfusion was performed after 2 days of washout followed by G-CSF. The period of bone marrow aplasia was uneventful.

At day 87 the second myeloablative course was given (repetition of the previous course), which was also uneventful, and treatment was completed in March 2004.

The CSF was examined after each cycle: after the first cycle cytology showed only one probably suspicious cell and all other subsequent cytological examinations were normal. The CT scan performed 3 months after completion of therapy did not show disease activity.

In the first year the patient was monitored on a monthly basis: he recovered completely from all complaints, regained a good shape and returned to work. The tumor markers in the plasma remained normal. In February 2005, 12 months after completion of therapy, CT scanning revealed an ongoing complete remission. Unfortunately, in March 2005 the patient was admitted by the emergency department with ischialgic pain in the right leg and relapse could be confirmed by cytologic examination of the CSF. Palliation was started with dexamethasone and radiotherapy to the involved lumbar spine. After 7 days he suddenly deteriorated and developed a clinical picture of an acute abdomen, probably gastric perforation. In the light of his dismal prognosis we decided not to perform surgery and 24 h later the patient died.

Discussion

This is the first report describing a patient with relapsed non-seminoma testis presenting with LC. We have demonstrated that a 1-year complete remission with high-dose systemic chemotherapy with autologous stem cell support can be achieved.

The overall prognosis for patients with a relapse of a metastatic TC is moderate with a 10–40% chance of long-term complete remission achieved with high-dose chemotherapy [1–5]. Moreover, as far as involvement of the CNS is concerned prognosis is poor when present at *initial diagnosis* and is even more dismal when occurring *during the course* of the disease, with a 5-year survival of only 2–5% [6,12].

Since literature on LC in relapsed TC is lacking, we will briefly review the literature concerning solid brain metastasis for a better understanding of its management and prognosis. This source of reference appears to be justified since TC represents a chemosensitive malignancy and both features comprise CNS involvement. In a

large retrospective series describing 139 TC patients from various institutions in Europe, no therapeutic benefit of additional radiotherapy after BEP chemotherapy in patients with *initial* brain metastases could be detected. However, for patients who developed brain metastasis *after* cisplatin-based induction chemotherapy an important beneficial role for cerebral radiotherapy was suggested [12]. Usually target doses of 10×3 or 20×2 Gy to the whole cerebrum appeared to be sufficient [13]. Our patient was treated with a comparable schedule. In the same series two dismal prognostic factors could be identified. First, the development of brain metastases *during* the course of the disease. This was associated with a worse 2-year survival of 15% as compared with 55% for those patients who presented with brain metastases initially. Second, the presence of extracerebral manifestations. This was associated with a 2-year survival below 5% as compared with 50% for those patients without extracerebral disease [12]. Hence, both dismal prognostic factors were present in our patient.

For patients with brain metastasis at *initial* presentation it appears that sufficient amounts of the drugs from the BEP regimen cross the blood–brain barrier, rendering intrathecal chemotherapy unnecessary. These suggestions are supported by the observation in 68 patients with primary germ cell tumors of the brain; 57% achieved a complete response by systemic chemotherapy alone [14]. However, in case of relapse with CNS involvement some studies report the absence of benefit of conventional chemotherapy and suggest that only palliative radiotherapy should be offered to these patients [2,4]. In our patient we could demonstrate that even in the case of *relapse* the application of systemic high-dose chemotherapy resulted in a 1-year complete remission.

As mentioned, knowledge about LC in TC is scarce, presumably since it is a rare phenomenon. For this reason knowledge of LC in other solid cancers is of importance to put things into perspective. LC occurs in approximately 5% of patients with cancer, and is increasingly diagnosed as patients live longer and as imaging techniques improve. The most common tumors involved are breast, lung and melanomas. Patients present with symptoms from injury to nerves, direct tumor invasion into the brain or spinal cord, obstruction of normal CSF flow pathways, or general interference with brain function. The diagnosis is most commonly made by cytology of the CSF. Radiologic studies may reveal subarachnoid masses, diffuse contrast enhancement of the meninges or hydrocephalus without a mass lesion. Without treatment, the median survival of patients with this disorder is 4–6 weeks. Early diagnosis and therapy is critical to preserving neurological function. Radiation therapy to involved/symptomatic sites increases the median survival to 3–6 months. The addition of intrathecal chemotherapy gives no additional benefit in terms of survival, but is responsible for a substantial increase in toxicity [8,9]. The major favorable prognostic factors include excellent performance status, absence of serious neurological deficits and absent or responsive systemic tumor [15]. Although our patient had systemic tumor and it had already relapsed, it still responded favorably to the chemotherapy-schedule applied. Apparently an adequate penetration in the CNS of these drugs was achieved, among which especially ifosfamide and thiotepa have been reported for this capability [6,12,16].

References

1 Beyer J, Kramar A, Mandanas R, Linkesch W, Greinix A, Droz JP, *et al.* High-dose chemotherapy as salvage treatment in germ cell tumors: a multivariate analysis of prognostic variables. *J Clin Oncol* 1996; **14**:2638–2645.

2 Schmoll HJ, Souchon R, Krege S, Albers P, Beyer J, Kollmannsberger C, *et al.* European consensus on diagnosis and treatment of germ cell cancer: a report of the European Germ Cell Cancer Consensus Group (EGCCCG). *Ann Oncol* 2004; **15**:1377–1399.

3 Broun ER, Nichols CR, Turns M, Williams SD, Loehrer PJ, Roth BJ, *et al.* Early salvage therapy for germ cell cancer using high dose chemotherapy with autologous bone marrow support. *Cancer* 1994; **73**:1716–1720.

4 Rick O, Bokemeyer C, Beyer J, Hartmann JT, Schwella N, Kingreen D, *et al.* Salvage treatment with paclitaxel, ifosfamide, and cisplatin plus high-dose carboplatin, etoposide, and thiotepa followed by autologous stem-cell rescue in patients with relapsed or refractory germ cell cancer. *J Clin Oncol* 2001; **19**:81–88.

5 Rodenhuis S, de Wit R, de Mulder PH, Keizer HJ, Sleijfer DT, Lalisang RI, *et al.* A multi-center prospective phase II study of high-dose chemotherapy in germ-cell cancer patients relapsing from complete remission. *Ann Oncol* 1999; **10**:1467–1473.

6 Spunt SL, Walsh MF, Krasin MJ, Helton KJ, Billups CA, Cain AM, *et al.* Brain metastases of malignant germ cell tumors in children and adolescents. *Cancer* 2004; **101**:620–626.

7 Mackey JR, Venner P. Seminoma with isolated central nervous system relapse, and salvage with craniospinal irradiation. *Urology* 1998; **51**: 1043–1045.

8 Bokstein F, Lossos A, Siegal T. Leptomeningeal metastases from solid tumors: a comparison of two prospective series treated with and without intra-cerebrospinal fluid chemotherapy. *Cancer* 1998; **82**:1756–1763.

9 Siegal T. Leptomeningeal metastases: rationale for systemic chemotherapy or what is the role of intra-CSF-chemotherapy? *J Neurooncol* 1998; **38**:151–157.

10 Pavlidis N. The diagnostic and therapeutic management of leptomeningeal carcinomatosis. *Ann Oncol* 2004; **15(suppl 4)**:285–291.

11 International Germ Cell Consensus Classification. A prognostic factor-based staging system for metastatic germ cell cancers. International Germ Cell Cancer Collaborative Group. *J Clin Oncol* 1997; **15**:594–603.

12 Fossa SD, Bokemeyer C, Gerl A, Culine S, Jones WG, Mead GM, *et al.* Treatment outcome of patients with brain metastases from malignant germ cell tumors. *Cancer* 1999; **85**:988–997.

13 Spears WT, Morphis JG, Lester SG, Williams SD, Einhorn LH. Brain metastases and testicular tumors: long-term survival. *Int J Radiat Oncol Biol Phys* 1992; **22**:17–22.

14 Balmaceda C, Heller G, Rosenblum M, Diez B, Villablanca JG, Kellie S, *et al.* Chemotherapy without irradiation–a novel approach for newly diagnosed CNS germ cell tumors: results of an international cooperative trial. The First International Central Nervous System Germ Cell Tumor Study. *J Clin Oncol* 1996; **14**:2908–2915.

15 Grossman SA, Krabak MJ. Leptomeningeal carcinomatosis. *Cancer Treat Rev* 1999; **25**:103–119.

16 Bokemeyer C, Nowak P, Haupt A, Metzner B, Kohne H, Hartmann JT, *et al.* Treatment of brain metastases in patients with testicular cancer. *J Clin Oncol* 1997; **15**:1449–1454.