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Case Report

High-dose chemotherapy with autologous peripheral blood stem cell support for recurrent primary AFP-producing intracranial germinoma

Hochdosischemotherapie mit autologem Stammzellsupport für Patienten mit AFP-produzierendem Germinom im Rezidiv

Abstract

We report of a 34-year old man with second intracranial relapse of a suprasellar germinoma. Despite of extensive pretreatment with radiation and conventional chemotherapy relapse occurred and was treated with sequential high-dose chemotherapy followed by transfusion of autologous peripheral stem cells. The high-dose chemotherapy course was complicated by refractory derailment of pineal gland insufficiency. The patient achieved a complete remission after high dose chemotherapy which lasted for 13 months. Subsequently, he developed a third relapse and died.

Zusammenfassung

Wir berichten über einen 34 Jahre alten Patienten mit zweitem intrakraniellem Rezidiv eines suprasellären Germinoms. Trotz intensiver Vorbehandlung mit Bestrahlung und konventioneller Chemotherapie kam es zum Rezidiv und der Patient wurde mit sequentieller Hochdosischemotherapie mit autologem Stammzellensupport behandelt. Während der Hochdosischemotherapie kam es zu einer refraktären Entgleisung einer Pinealdrüsen-Insuffizienz. Der Patient erreichte eine komplette Remission nach Hochdosischemotherapie, die für 13 Monate anhielt. Er starb nach diesem Zeitraum im Rahmen des dritten Rezidivs.

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Introduction

Tumors of the pineal gland are rare accounting for 0.4 - 1% of all primary tumors of the brain [1]. Different tumor types are found in the pineal region: tumors that derive from germ cells (germinomas and "non-germinomatous" germ cell tumors like embryonic carcinomas and teratomas), from parenchymal cells (pinealoblastomas and pineocytomas), and from glial cells are encountered as well as lesions that represent non neoplastic cysts [2]. In all series germ cell tumors represent the most common histology (60%) [2]. The peak incidence of germ cell tumors is in the second decade [3]. In contrast to the other tumors mentioned which have no sex preference, germ cell tumors are more frequent in men than in women [1]. First symptoms are often neurological signs and complaints caused by an obstructive hydrocephalus with headache, nausea, and vomiting and/or involvement of ocular pathways. Determination of histology, tumor markers in serum and CSF, and extent of disease are critical for optimal management of pineal region tumors. Five year survival rates following radiation range from 44

- 78% and depend on extent of disease, age, radiation volume and dose to the primary site but primarily on histology [4]. The five year survival of patients with germinoma is 76% as compared with 21% for those with a "non-germinomatous" germ cell tumor.
There is no established therapy for relapsing or refractory intracranial germinoma. In analogy to germinomas of the testis a higher curability may be expected with high dose chemotherapy followed by autologous blood stem-cell retransfusion [5]. For non germinomatous tumors no guidelines exist with respect to dosage, combination or sequence of chemotherapy and radiation.

Case presentation

A 25-year old man became symptomatic by diabetes insipidus. Further examination revealed that these symptoms were caused by a primary AFP producing germinoma of the pineal gland. The initial treatment in 1987 consisted of radiation of the tumor with 30 Gy which resulted in a complete remission.
Seven years later he developed a first relapse in the anterior section of the first ventricle with infiltration of brain parenchyma, and extension to the intradural and extradural lumbosacral spinal canal. The spinal tumor was irradiated with 30 Gy. Immediately after radiation he was treated with high dose methotrexate 12 g/m² i.v. on day 1 (total dose 20 g). Three weeks later chemotherapy according to the PEB-protocol was initiated: cisplatin 20 mg/m² i.v. d1-d5, etoposide 100 mg/m² i.v. d1-d5, and bleomycin 30 mg i.v. d1, 8, and 15. Four cycles were administered. In order to prevent bleomycin induced lung damage bleomycin was replaced by ifosfamide 1200 mg/m² i.v. twice daily (d1-d5) in two additional cycles. These six cycles resulted in a total dose of cisplatin 1070 mg, etoposide 4800 mg, bleomycin 395 mg, ifosfamide 24.5 g. Staging three weeks after termination of the chemotherapy showed a complete remission of the brain lesion. Residual masses in the spinal areas were interpreted as representing most likely a scar. AFP had returned to normal values.
Another 10 months later the patient suffered from a second relapse localized again in the anterior section of the ventricle at the same location as the first relapse and additionally in the roof of the left ventricle. The spinal tumors had an equal size compared to prior relapse. The AFP level at this time was increased up to 69 U/l.
The patient was treated with a high dose chemotherapy followed by retransfusion of autologous stem cells. Stem cell harvesting was successful after one cycle according to the PEI-protocol with cisplatin 25 mg/m² i.v. twice daily d2-4 (total dose 170 mg), etoposide 100 mg/m² i.v. once daily d1-d5 (total dose 860 mg), and ifosfamide 1.5 g twice daily i.v. d1-d5 (total dose 13 g). From day 10 the patient received filgrastim (Neupogen®) 5 µg/kg s.c. for stem cell mobilisation. The harvest of three apheresis were enough for performing two cycles of high dose chemotherapy (>2 x 10^6 CD 34 pos. cells/kg). After hematologic reconstitution the patient underwent two cycles of high dose chemotherapy according to the CEI-protocol (cumulative dose of carboplatin 375 mg/m² i.v.) twice daily d1-d5 (total dose of two cycles 5000 mg), etoposide 310 mg/m² i.v. twice daily d1-d5 (total dose of two cycles 4100 mg), and ifosfamide 2.5 g/m² i. v. twice daily (total dose of two cycles 33 g) each followed by reinfusion of autologous peripheral blood stem cells. The two cycles were completed within 36 days. The patient remained aplastic (WBC < 1G/l, thrombocytes <20 G/l) for 7 and 9 days, respectively. After treatment AFP decreased to 9.6 U/ml and the tumor manifestation in the brain disappeared. Again the lesions in the spinal areas were constant in size.
The therapy was complicated by a global insufficiency of the pineal gland. Since first cranial radiation he received antidiuretic hormones (ADH) applied as a nasal spray. During the high dose chemotherapy with fluid intakes up to 4 liter - to prevent cisplatin induced renal damage - his urine production increased up to 13 liter/24 hours after therapy. This pattern was refractory under increase of ADH, and under substitution of mineralocorticoids. The serum electrolytes remained stable under substitution. After termination of chemotherapy the urine production went back to normal. Other endocrinologic functions remained stable during chemotherapy.
The patient remained in stable remission for a period of 13 months until a third relapse. The tumor was then localized in the roof of the left ventricle and in the brain stem. This third relapse was complicated by seizures which resolved under high dose dexamethasone therapy. Because of extensive pretreatment with chemotherapy the patients underwent cerebral radiation with another 30 Gy, so the total dose to the brain was 60 Gy. Despite slow reconstitution of the performance status the patient died one month later at home most likely due to an electrolyte derailment.

Discussion

Despite of considerable advances in the treatment of patients with germ cell tumors, certain patients, especially those who relapse after radiation and/or chemotherapy fare poorly [6] [7]. Guidelines have not yet been defined for therapy of relapsed and/or refractory germinoma of the pineal gland. Considering that germ cell tumors of the pineal gland have biological similarities to germ cell tumors of the testis, the patient was treated at second relapse with high dose chemotherapy and stem cell support in analogy to treatment protocols for systemic germ cell tumors [5].
To date there are no reports on adult patients with relapse of a pineal germinoma treated with high dose chemotherapy and stem cell transplantation. Kimura et al reported of a patient with a primary β-HCG producing cerebral germinoma who gained a complete remission after high dose chemotherapy and autologous bone marrow transplantation [8]. Graham et al reported about a heteroge-

neous group of brain tumors in 49 children (two children with germ cell tumors) treated with different high dose chemotherapy regimens followed by autologous marrow rescue [9]. Both children were alive and had no evidence of disease 30 and 20 months respectively after treatment. In contrast to the here reported patient both children were treated with high dose chemotherapy and marrow rescue as first line treatment because of high risk of recurrence.

Our patient remained in stable complete remission for 13 months after high dose chemotherapy with autologous stem cell support. Most likely due to the high curability rate of intracerebral germinoma with conventional therapy and/or radiation there are no published data of survival or disease free survival times after tumor recurrence for conventional therapy. However, in the most cases the duration of second or third remission is shorter than the first remission. The third remission gained after high-dose chemotherapy and stem cell transplantation had a three months longer duration than his second remission.

High-dose chemotherapy with autologous stem cell support is a potentially curative treatment for patients with relapsed or high risk (metastatic disease) germinomas of the pineal gland. According to data from other tumor entities, the response to chemotherapy seems to be the best prognostic factor.

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