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Case report

Recurrent disseminated retinoblastoma in a 7-year-old girl treated successfully by high-dose chemotherapy and CD34-selected autologous peripheral blood stem cell transplantation

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Summary:

A localized retinoblastoma of the left eye in a 7-year-old girl, was treated by enucleation. She received no additional therapy. Four months later, metastases of retinoblastoma in the lymph nodes, bone and bone marrow were diagnosed. Relapse chemotherapy consisting of three courses of vincristine, cyclophosphamide, etoposide and carboplatin led to a second complete remission. Subsequent high-dose chemotherapy with thiotepa, etoposide and carboplatin and autologous stem cell transplantation with CD34-selected stem cells were successful, with no adverse effects. No radiotherapy was given and the girl remains in continuous second remission with a follow-up of more than 4 years. *Bone Marrow Transplantation* (2001) **27,** 653–655.
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The prognosis of retinoblastoma with haematogenous spread into bone or bone marrow is very poor.[1] There are only a few reports of successful therapy for disseminated retinoblastoma.[2–4] We describe the case of a 7-year-old girl suffering from relapse of retinoblastoma with metastases in lymph nodes, bone and bone marrow. After treatment, including high-dose chemotherapy, the girl remains in continuous second remission with a follow-up of more than 4 years.

Case report

A seven-year-old girl suspected of having retinoblastoma presented with a 3-week history of leucokoria and divergent strabism of her left eye. The right eye was normal on examination. No cases of retinoblastoma have occurred in her family to date. On tomography and magnetic resonance imaging (MRI), there was no evidence of extraocular extension, invasion of the optic nerve, or metastases. Enucleation of the left eye was performed. Histological examination revealed a poorly differentiated retinoblastoma with marked choroidal infiltration, but no signs of invasion of the optic nerve or involvement of the sclera. There was no evidence of recurrence in the left orbit or of development of a retinoblastoma in the right eye on subsequent examinations. The girl was given no further treatment. Four months later, a pre-auricular tumour on the left, 1.5 cm in diameter, was observed. The tumour was excised and histopathological examination showed metastatic infiltration of a lymph node with retinoblastoma cells. Bone marrow aspiration was also positive for retinoblastoma cells. Bone scintigraphy showed pathological enhancement in the area of the left temporal skull and in the third thoracic vertebra. MRI of the head and vertebral column showed evidence of metastatic lymphadenopathy in the left pre-auricular region and along both carotid arteries, together with small metastases in the left fronto-temporal, temporal and right parietal skull bones. In addition, there were metastatic lesions of the fourth, fifth and eighth throracic vertebrae as well as of the third lumbar vertebra (Figure 1A). The spinal fluid was free of retinoblastoma cells. In summary, the girl suffered from a metastatic relapse of her retinoblastoma with infiltration of lymph nodes, bones and the bone marrow.

Chemotherapy given as described by Bornfeld *et al,*[5] using three courses of vincristine (1.5 mg/m^2), cyclophosphamide (1200 mg/m^2), etoposide (450 mg/m^2) and carboplatin (300 mg/m^2) every 3 weeks, led to complete remission of the bone marrow infiltration. After the third course, stem cell mobilisation was performed giving rhuG-CSF (Neupogen) 10 μg/kg/day subcutaneously for 12 days. Apheresis was performed with a Cobe Spectra. For positive selection of CD34$^+$ haematopoetic stem cells, the Cellpro method was used. After stem cell selection, a fourth course of chemotherapy was given.

Three weeks later, the girl received high-dose chemotherapy. Thiotepa at a dose of 3×300 mg/m^2 i.v. over 1 h from days −8 to −6 was followed by etoposide (1000 mg/m^2 i.v. over 4 h on day −5) and carboplatin

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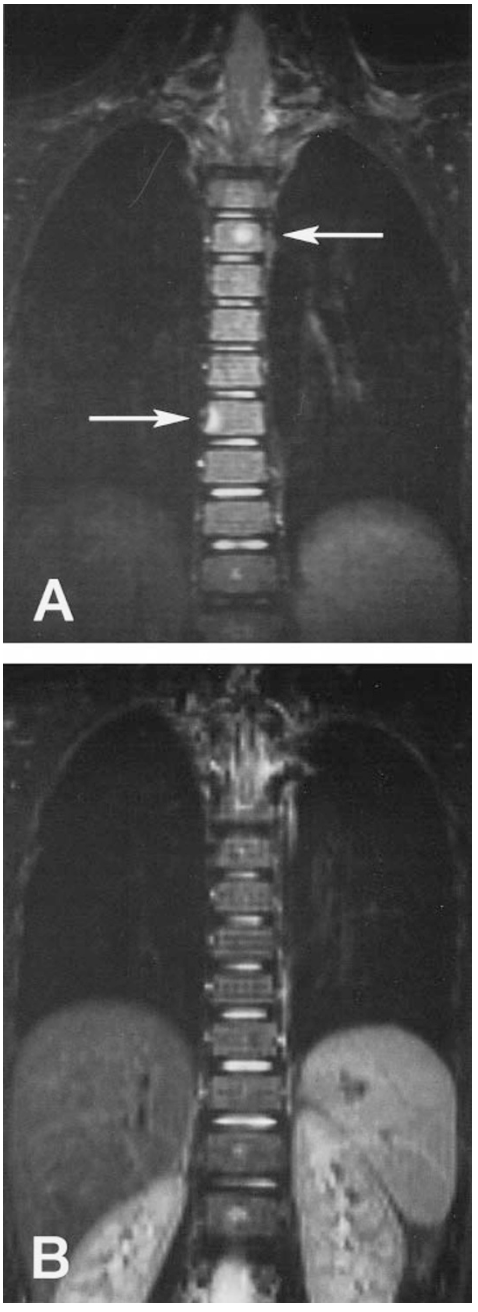

Figure 1 (**A**) Bone and bone marrow infiltration of the vertebral bodies with retinoblastoma cells (arrows). (**B**) Disappearance of the vertebral infiltration with retinoblastoma cells 5 months after starting therapy.

(3×500 mg/m^2 i.v. over 2 h from days −4 to −2). On day 0 1.6×10^6 CD34$^+$ stem cells/kg body weight was infused. The clinical course post transplant was uneventful, except for a mild fever from day +4 until day +6, mucositis from day +0 until day +13, and diarrhea from day −3 until day +13.

On day +22, the white blood cell count recovered to 1×10^9/l and the neutrophil count to 0.5×10^9/l. The platelet count on day +27 was 14.0×10^9/l and she received her last platelet transfusion. After day +27 the platelet count rose spontaneously for the first time to values over 100×10^9/l 3 months after stem cell transplantation. The last transfusion of red blood cells was required on day +68, at which time her haemoglobin value was 7.2 mg/dl. No further transfusions were necessary. She did not receive additional irradiation to the lymph nodes metastases or to the bones. The metastatic lesions of the vertebrae disappeared completely within 5 months (Figure 1B). After 3 years follow-up, the patient had evidence of hypergonadotropic hypogonadism with an elevated serum level of follicle stimulating hormone and decreased level of oestradiol. No additional late toxicities have been observed. She is in continuous second remission with a follow-up of more than 4 years.

Discussion

Retinoblastoma with haematogenous metastases continues to be a difficult therapeutic problem. In spite of intensive conventional chemotherapy and irradiation such patients are rarely cured.[6] Irradiation of the orbit may be useful in patients with isolated metastases in the orbit or initial infiltration of the optic nerve.[4] High-dose chemotherapy with autologous stem cell rescue can improve the prognosis of retinoblastoma patients with bone metastases, but despite high-dose chemotherapy and additional irradiation, a high incidence of relapse in the central nervous system (CNS) is described in the literature in patients, where the bone relapse site was the skull bones or the bone marrow.[4] The spinal fluid of our patient was free of tumour cells, but because she had multiple metastases of the skull and the vertebral column, we felt we needed to minimise the risk of CNS relapse, at the same time minimising the risk of developing severe side-effects. Therefore, we use a preparative regimen for peripheral blood stem cell transplantation containing thiotepa, etoposide and carboplatin. We avoided using irradiation of the CNS and of the vertebral metastases because of the risk of neurologic side-effects involving the spinal cord and the risk of developing a second malignancy.

Thiotepa was chosen due to its excellent penetration into the spinal fluid.[7] Similar high-dose chemotherapy with thiotepa, etoposide and carboplatin has already been used in the treatment of brain tumours.[8,9]

To reduce the risk of tumour cell reinfusion, positive selection with the Cellpro method for autologous CD34$^+$ peripheral blood stem cells was performed. This method is described as being effective in purging tumour cells from the leukapheresis products of patients with stage 4 neuroblastoma.[10] Haematopoietic recovery was slightly delayed. This was probably due to the low stem cell number of 1.6×10^6 CD34$^+$ cells/kg body weight. Fortunately, complete haematological recovery was achieved and severe complications did not occur during the post-transplant course of our patient. As a late effect of therapy, gonadal dysfunction was diagnosed. This is a well known late effect of cyclophosphamide, carboplatin and etoposide therapy used for relapse and high-dose etoposide and high-dose carboplatin used in the myeloablative setting.[11] Additional late toxicities were not observed with a follow-up of more than 4 years.

We conclude that chemotherapy with VCR, cyclophosphamide, etoposide and carboplatin followed by a mye-

loablative regimen containing thiotepa, etoposide and carboplatin have curative potential in disseminated retinoblastoma and avoid the toxic side-effects associated with irradiation.

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