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Case report

High-dose chemotherapy with hematopoietic stem cell transplantation in adults with bone marrow relapse of medulloblastoma: report of two cases

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Summary:

Extraneural relapses of medulloblastoma are associated with a very poor outcome. We present two cases of young adults who developed bone marrow metastases after treatment of medulloblastoma. A very good response to a sequentially scheduled combination of carboplatin and etoposide was observed. Then, high-dose chemotherapy was delivered consisting of busulfan and thiotepa followed by infusion of autologous hematopoietic stem cells. Toxicity of the conditioning regimen was acceptable. The patients remained free of disease 20 and 27 months from the time of relapse, respectively. Further studies are needed to evaluate the impact of high-dose chemotherapy in terms of survival of such patients.

Keywords: adult medulloblastoma; metastases; chemotherapy; autologous stem cell transplantation

Medulloblastoma, a malignant tumor originating in the cerebellum, generally occurs in the first decade of life. It is a rare disease in the adult population and represents less than 1% of adult brain tumors. Extraneural relapses of medulloblastoma represent 7 to 13% of recurrences and are associated with a very poor outcome.[1] Encouraging preliminary data have been reported in children with recurrent malignant brain tumors receiving high-dose chemotherapy with autologous bone marrow rescue.[2,3] We report two young adults who underwent autologous hematopoietic stem cell transplantation for bone marrow relapse of medulloblastoma.

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Case reports

Patient 1

In July 1995, a non-metastatic cerebellar medulloblastoma was diagnosed in a 22-year-old man. The tumor was totally resected and cranio-spinal radiation therapy was given postoperatively. Fifteen months later the patient complained of left hip pain. A pelvic magnetic resonance (MR) scan revealed diffuse low intensity signals on T1-weighted images, high intensity signals on T2-weighted images in the bone marrow of the left acetabulum and the body of the left ilium with enhancement after gadolinium administration (Figure 1a). An open biopsy of the left ilium and a bone marrow biopsy of the right posterior iliac crest revealed marrow involvement with metastatic medulloblastoma cells. No evidence of recurrent tumor within the central nervous system was demonstrated. Combination chemotherapy consisting of carboplatin (160 mg/m^2/day) and etoposide (100 mg/m^2/day) for 5 days was administered. Cycles were repeated at 4 weekly intervals. The patient was symptom-free after the first course of chemotherapy. Bone marrow biopsy was normal after the second course of chemotherapy. He received a total of five courses of carboplatin-etoposide. There were no episodes of febrile neutropenia. The main toxicities were nausea and myelosuppression. After the fifth course of chemotherapy, MR revealed marked improvement in the left ilium and left acetabulum bone marrow signals (Figure 1b). Cytapheresis was performed after a 3 g/m^2 cyclophosphamide infusion followed by G-CSF administration, leading to the collection of 2×10^6 CD34 cells/kg (before cryopreservation) and 8.5×10^4 CFU-GM/kg (after thawing). High-dose chemotherapy (HDC) was administered in September 1997, consisting of busulfan 4 mg/kg p.o in four divided doses daily for 4 days (total dose 16 mg/kg) and thiotepa 300 mg/m^2 once daily i.v for 3 consecutive days (total dose 900 mg/m^2) followed by infusion of autologous hematopoietic stem cells. Grade 3 mucositis without severe septic complications occurred. Duration of granulocytopenia (less than 0.5×10^9/l) and thrombocytopenia (less than 50×10^9/l) was 10 and 12 days, respectively. The patient was discharged from the hospital 13 days after hematopoietic stem

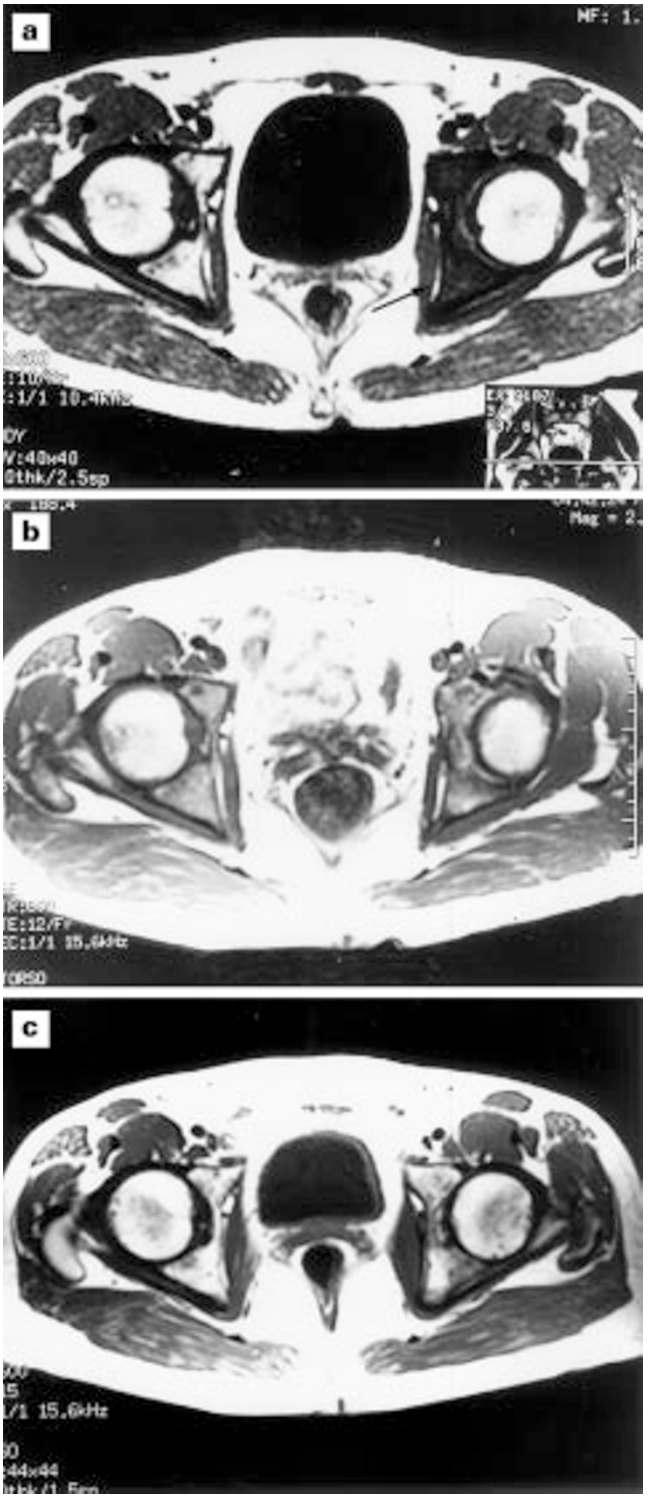

Figure 1 T1-weighted axial MR image of the pelvis at initial diagnosis shows involvement of the right iliac bone marrow (arrow) with preservation of the bony cortex (**a**). Pre-transplant (**b**) and post-transplant (**c**) images show a progressive decrease in the size of the lesion.

cell transplantation. Seventeen months after HDC, physical examination was normal and MR showed occasional foci of abnormal bone marrow signal in the left ilium (Figure 1c).

Patient 2

In September 1995, a 30-year-old male underwent total excision of a non-metastatic cerebellar medulloblastoma. Post-operative treatment consisted of cranio-spinal irradiation. In January 1997, he developed episodes of pain in the lower lumbar vertebral area, which progressed over the next few months. In June 1997, an MR scan of the pelvis and the rachis revealed low intensity signal T1-weighted images, high intensity signal on T2-weighted images in the bone marrow of lumbar vertebrae, right ilium, left acetabulum and sacrum with enhancement after administration of gadolinium. A bone marrow biopsy of the right posterior iliac crest revealed marrow involvement with metastatic medulloblastoma cells. No evidence of cerebral or spinal-axis recurrence of the tumor could be demonstrated. The patient was treated with combination chemotherapy consisting of carboplatin (120 mg/m^2/day) and etoposide (75 mg/m^2/day) for 5 days. He became symptom-free after the first course of chemotherapy. Bone marrow biopsy was normal after the second course of chemotherapy. He received a total of seven courses of carboplatin-etoposide. The main toxicities were nausea and myelosuppression. There were no episodes of febrile neutropenia. After the seventh course of chemotherapy, MR revealed marked improvement in the lumbar vertebrae and pelvic bone marrow signals. Cytapheresis was performed after G-CSF (10 μg/kg/day) alone leading to the collection of 0.55×10^6 CD34 cells/kg (before cryopreservation) and 1.2×10^4 CFU-GM/kg (after thawing). In addition 1.89×10^6 CD34 cells/kg (before cryopreservation) and 4.1×10^4 CFU-GM/kg (after thawing) were collected from bone marrow. High-dose chemotherapy was administered in July 1998, consisting of busulfan 4 mg/kg p.o in four divided doses daily for 4 days (total dose 16 mg/kg) and thiotepa 300 mg/m^2 once daily i.v for 3 consecutive days (total dose 900 mg/m^2) followed by infusion of autologous hematopoietic stem cells. A grade 3 mucositis without severe septic complications occurred. The duration of granulocytopenia (less than 0.5×10^9/l) was 10 days while thrombocytopenia (less than 50×10^9/l) persisted for 5 months post transplantation. The patient was discharged from the hospital 14 days after hematopoietic stem cell transplantation. Seven months after HDC, physical examination was normal and MR showed occasional foci of abnormal bone marrow signal in the left ilium and sacrum.

Discussion

Medulloblastoma is one of the most common primary brain tumors in children but is rare in adults. The reported progression-free survival rates between children and adults are comparable.[4–6] Surgery followed by craniospinal irradiation is considered as the standard treatment in adult patients with medulloblastoma. In a retrospective study of 156 cases of medulloblastoma in patients older than 18 years of age, no benefit from concomitant chemotherapy was demonstrated.[5] However, two randomized multicenter trials demonstrated the benefit of adjuvant chemotherapy in term of event-free survival in children with extensive medulloblas-

toma.[6,7] Some studies suggested that adjuvant chemotherapy decreases the subsequent risk of extraneural disease including metastasis to bone.[8]

The prognosis for patients with extraneural relapse is poor, with a median survival of 5 to 10 months.[1] Bone metastases from medulloblastoma most commonly involve the axial skeleton, particularly the pelvis and vertebrae. In the present cases, bone marrow involvement by the malignant process resulted in abnormal signals when MR imaging was used. By contrast to our findings, Olson *et al*[9] reported a low signal intensity on T1-weighted and T2-weighted MR scans without contrast enhancement. However, the MR characteristics of bone marrow metastases from medulloblastoma are very rarely described and it is difficult to draw any conclusion from this discrepancy.

Medulloblastoma is a chemotherapy-sensitive tumor even in recurrent metastatic situations. Carboplatin and etoposide as single agents are reported to result in partial or complete remission in 28% and 67% of metastatic pediatric patients, respectively.[10] Complete or partial remissions were observed in 53% of 15 patients with newly diagnosed high-risk medulloblastoma receiving pre-irradiation chemotherapy with carboplatin and etoposide.[11] In the present cases, combination of these two agents was successfully used in initiating remission. Interestingly, hematologic toxicity from this chemotherapy was acceptable in our previously irradiated patients. In spite of an initially favorable antitumor response, the combination of chemotherapeutic agents has mainly offered palliative benefits in patients with systemic relapse from medulloblastoma and very few patients are long-term survivors. Our patients were in clinical and marrow remission after two courses of carboplatin-etoposide and they subsequently received three to five courses without disease recurrence. However, we chose to pursue an aggressive strategy consisting of HDC with hematopoietic stem cell transplantation. Ablative bone marrow chemotherapy followed by hematopoietic stem cell rescue has been administered to some patients with relapsed medulloblastoma to improve tumor cell kill. Lundberg *et al*[12] reported the case of a 27-year-old male with recurrent metastatic medulloblastoma treated with multi-agent chemotherapy followed by allogeneic bone marrow transplantation (BMT) from an HLA-identical sibling donor. This patient is in complete remission 28 months after BMT with an excellent performance status. High-dose chemotherapy with autologous BMT support resulted in a high response rate (75%) in a series of 20 children with relapse of medulloblastoma.[3] However, among the seven children with metastatic disease enrolled in this study, only one is alive with a follow-up of 13 months. Our patients had minimal residual disease defined as residual foci of abnormal bone marrow MR in the pelvis prior to transplantation. These lesions regressed during the post-transplant follow-up period.

In conclusion, our data support the use of carboplatin in combination with etoposide as a first-line regimen in adults with bone marrow involvement by medulloblastoma. High-dose chemotherapy with busulfan and thiotepa followed by autologous hematopoietic stem cell transplantation was tolerable in these previously irradiated patients. Extended follow-up is required to determine the value of such a strategy.

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References

1 Rochkind S, Blatt I, Goldhammer Y. Extracranial metastases of medulloblastoma in adults: literature review. *J Neurol Neurosurg Psych* 1991; **54**: 80–86.
2 Finlay JL, Goldman S, Wong MC *et al*. Pilot study of high-dose thiotepa and etoposide with autologous bone marrow rescue in children and young adults with recurrent CNS tumors. *J Clin Oncol* 1996; **14**: 2495–2503.
3 Dupuis-Girod S, Hartmann O, Benhamou E *et al*. Will high-dose chemotherapy followed by autologous bone marrow transplantation supplant cranio-spinal irradiation in young children treated for medulloblastoma? *J Neuro Oncol* 1996; **27**: 87–98.
4 Prados MD, Warnick RE, Wara WN *et al*. Medulloblastoma in adults. *Int J Radiat Oncol Biol Phys* 1995; **32**: 1145–1152.
5 Carrie C, Lasset C, Alapetite C *et al*. Multivariate analysis of prognostic factors in adults patients with medulloblastoma. *Cancer* 1994; **74**: 2352–2360.
6 Evans AE, Jenkin RD, Sposto R *et al*. The treatment of medulloblastoma: results of a prospective randomized trial of radiation therapy with and without CCNU, vincristine and prednisone. *J Neurosurg* 1990; **72**: 572–582.
7 Tait DM, Thornton-jones H, Bloom HJ *et al*. Adjuvant chemotherapy for medulloblastoma: the first multi-centre control trial of the International Society of Paediatric Oncology. *Eur J Cancer* 1990; **26**: 464–469.
8 Harstell WF, Montag AG, Lydon J *et al*. Treatment of medulloblastoma in adults. *Am J Clin Oncol* 1992; **15**: 207–211.
9 Olson EM, Tien RD, Chamberlain MC. Osseous metastasis in medulloblastoma: MRI findings in an unsual case. *Clin Imag* 1991; **15**: 286–289.
10 Leo E, Schlegel PG, Lindemann A. chemotherapeutic induction of long term remission in metastatic medulloblastoma. *J Neuro Oncol* 1997; **32**: 149–154.
11 Heidman RL, Kovnar EH, Kellie SJ *et al*. Preirradiation chemotherapy with carboplatin ant etoposide in newly diagnosed embryonal pediatric CNS tumor. *J Clin Oncol* 1995; **13**: 2247–2254.
12 Lundberg JH, Weissman DE, Beatty PA, Ash RC. Treatment of recurrent metastatic medulloblastoma with intensive chemotherapy and allogeneic bone marrow transplantation. *J Neuro Oncol* 1992; **13**: 151–155.