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LETTER TO THE EDITOR

Antitumor effect of allogeneic hematopoietic SCT in metastatic medulloblastoma

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Clinical studies of non-myeloablative allogeneic hematopoietic SCT (NST) have demonstrated that donor lymphocytes transferred with the graft may produce a clinically meaningful antitumor effect (graft-versus tumor) in recipients with renal cell cancer or other solid tumors refractory to conventional treatments.[1,2] Few data are currently available in this field in patients with medulloblastoma. Matsuda *et al.*[3] reported one child who obtained a short-lasting PR following allogeneic hematopoietic SCT for relapsed medulloblastoma. Lundberg *et al.*[4] reported one patient who achieved CR lasting more than 2 years following allogeneic hematopoietic SCT for recurrent metastatic medulloblastoma. However, a clear graft-versus tumor effect cannot be ruled out in these patients as they received myeloablative high doses of chemotherapy as the conditioning regimen, which might *per se* be responsible for tumor response. In this article, we report a durable complete tumor response following NST in a person with metastatic medulloblastoma.

In 2002, a 25-year-old woman was referred to our institution for relapsed medulloblastoma (stage IV, World Health Organization Classification) and was previously treated with radical surgery and adjuvant craniospinal radiotherapy. The patient had grade IV thrombocytopenia and grade III anemia requiring RBC transfusions. Complete restaging documented medulloblastoma BM involvement by trephine core biopsy and no other sites of recurrence. The patient was given conventional chemotherapy (CY, etoposide and cisplatin) with a clinical benefit (progressive reduction in transfusion requirement – Figure 1) and biopsy-proven persistence of BM involvement (Figures 2a–c). Because of the poor prognosis of recurrent medulloblastoma with expected short-term survival and the lack of alternative therapeutic option (intensified chemotherapy with autologous stem cell support[5] was excluded owing to marrow involvement), the patient gave written informed consent to be treated according to a phase I NST protocol for refractory solid tumors approved by the Ethical Committee of Ospedale Niguarda Ca' Granda.[6]

In March 2003, the patient received a pre transplant conditioning regimen consisting of IV thiotepa (300 mg/m^2) on day −5, CY (30 mg/kg daily) and fludarabine (30 mg/m^2 daily) on days −4 and −3. On day 0, 6.62×10^6 filgrastim mobilized CD34+ cells and 4.4×10^8 CD3+ cells/kg recipient, collected from the 25-year-old HLA identical brother, were transplanted into the patient.[7] Immunosuppression for GVHD prophylaxis consisted of CYA and short-course MTX. Antimicrobial therapy followed institutional protocols consisting of itraconazole for antifungal prophylaxis, acyclovir for antiviral prophylaxis and levofloxacin for antibacterial prophylaxis. The degree of donor–recipient chimerism in both myeloid and T-cell lineages was assessed by PCR assay of minisatellite regions.

Hematopoietic engraftment was achieved on day +13, and early post transplant course was uneventful. CYA administration was tapered and discontinued on day +80, in the absence of acute GVHD and with 100% T-cell donor chimerism, which was confirmed on subsequent controls. BM biopsy performed on day +120 (Figures 2b–d) showed CR of medulloblastoma infiltration. On day +110, 30 days after discontinuation of CYA, she developed grade II/III hepatic GVHD that was confirmed by liver biopsy. The patient was treated with steroids and extracorporeal photopheresis[8] with full recovery. Six months following transplant, she developed extensive chronic cutaneous and mucosal GVHD. Oral prednisone and subsequently CYA were given and since then she has required immunosuppressive treatment at doses depending on the clinical behavior of GVHD. In August 2006, the patient developed muscle weakness; antinuclear antibody test result elevated (>1:640) and musculoskeletal biopsy allowed for the diagnosis of dermatomyositis. Low-dose MTX was introduced with muscle strength improvement and normalization of antinuclear antibody test. At present, approaching 5 years from NST, the patient is in CR, with extensive chronic cutaneous GVHD requiring immunosuppressive therapy.

Because of the poor prognosis of recurrent metastatic medulloblastoma,[9] the long-lasting remission obtained in this patient can only be attributed to the antitumor effect generated by the donor's immune system. Unfortunately, the graft-versus tumor effect was associated with the occurrence of chronic GVHD, a complication that, as in this case, can significantly impair patient's quality of life.

We believe that this pilot treatment experience suggests that NST is an approach to be considered for selected patients with relapsed metastatic medulloblastoma and an otherwise poor prognosis who have an HLA identical sibling. This is also in light of most recent advances in the prophylaxis and treatment of GVHD.[10]

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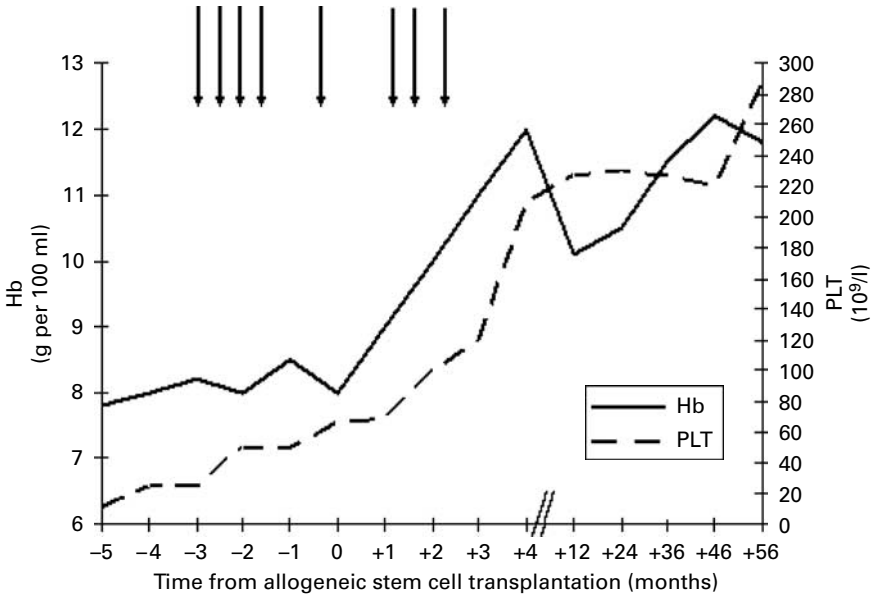

Figure 1 Normalization of RBC and platelet counts in peripheral blood and reversal of RBC transfusion requirements after non-myeloablative allogeneic hematopoietic SCT. Hb levels refer to the lowest levels before RBC transfusion. Each black arrow refers to two packed RBC units.

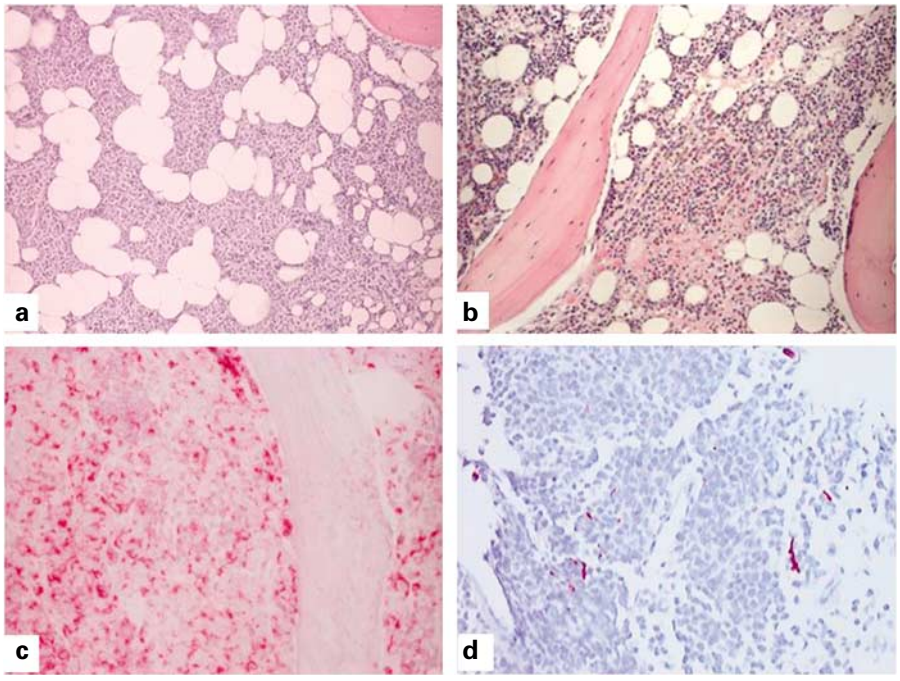

Figure 2 Microscopic evaluation of BM biopsies before (**a** and **c**) and 4 months after allogeneic hematopoietic SCT (**b** and **d**). Panels a and c show medulloblastoma cell infiltration assessed by standard hematoxylin–eosin and glial fibrillary acidic protein immunohistochemistry stain, respectively. Panels b and d show normal hematopoietic cells and lack of BM infiltration by medulloblastoma cells assessed by the same methods of panels a and c, respectively. Figures show representative fields at $\times 200$ (**a** and **b**) or $\times 400$ (**c** and **d**) magnifications.

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