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BONE MARROW TRANSPLANTATION FOR REFRACTORY LANGERHANS' CELL HISTIOCYTOSIS

*Valentino Conter, Agrippino Reciputo, Chiara Arrigo, Nadia Bozzato, Alessandra Sala, Maurizio Aricò**

*Department of Pediatrics, University of Milan, Ospedale S.Gerardo, Monza; *Department of Pediatrics, University, IRCCS Policlinico S. Matteo, Pavia, Italy*

ABSTRACT

Langerhans' cell histiocytosis (LCH) is an uncommon disorder of childhood, formerly referred to histiocytosis X. A significant proportion of children with disseminated disease may undergo progression to a fatal outcome despite chemotherapy with single or multiple agents. Only six cases of LCH treated with BMT have been reported in the literature, including two cases of autologous BMT. Of them, only one was less than 14 years of age. We describe a 4-year-old child whose disseminated, refractory Langerhans' cell histiocytosis was not controlled by front-line monotherapy with etoposide, nor by rescue treatment with combined chemotherapy (vinblastine and etoposide) and immunotherapy (steroids and cyclosporine). Due to the high risk of fatal progressive disease, he underwent bone marrow transplantation from his HLA-identical sister who was heterozigous for β-thalassemia. On day 24 after transplantation marrow reconstitution was evident, with WBC count 2.3×10^9/L, neutrophil count $>0.5\times10^9$/L, and platelet count 72×10^9/L. Engraftment was demonstrated by PCR DNA analysis. The patient was discharged on day 25. After transplantation he experienced fever for 11 days and developed signs of grade I cutaneous and intestinal graft-versus-host disease, that was treated with methylprednisolone from days 11 to day 68 (1 mg/kg/day for 18 days, then tapered). He became transfusion independent on day 24; the hemoglobin value was 7.5 g/dL on day 54 and has remained >10 g/dL since day 200. Features of heterozygous β-thalassemia have been evident since then. Bone marrow aspirate was normal on days 25 and 94. At the time of this writing he remains in excellent condition, disease and treatment free, 25 months after transplantation. Although limited, current experience suggests that bone marrow transplantation has the potential to cure refractory Langerhans' cell histiocytosis.

Key words: Langerhans' cell histiocytosis, bone marrow transplantation, chemotherapy

Langerhans' cell histiocytosis (LCH) is a rare disorder with variable clinical manifestations.[1,2] Although patients with localized disease may show an excellent outcome with minimal or no treatment, a significant proportion of children with disseminated disease may undergo progression to a fatal outcome despite chemotherapy[3] and immunotherapy.[4]

Allogeneic bone marrow transplantation (BMT) has been employed in some non malignant disorders including histiocytosis.[5,6] Since LCH derives from hyperactivation and proliferation of macrophage progeny cells, there is a rationale for using BMT to treat advanced, resistant LCH. Only six such cases have been reported in the literature,[7-9] including two cases of autologous BMT. Of them, only one was less than 14 years of age.

We describe a 4-year-old child whose disseminated, refractory LCH was not controlled by chemotherapy and immunotherapy. Due to the high risk of fatal progressive disease, he under-

Correspondence: Dr. Maurizio Aricò, Department of Pediatrics, University, IRCCS Policlinico S. Matteo, 27100 Pavia. Italy. Fax: international +39.382.502601. E-mail: aricom@ipv36.unipv.it.
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went BMT from his HLA-identical sister. The patient is asymptomatic and disease free at 25 months after the transplantation.

Case report

G.L., male, was the third child of healthy unrelated parents. At 16 months he developed skin rash, lymphadenomegaly, splenomegaly and anemia (5.9 g/dL). Lymph node biopsy was diagnostic for LCH on the basis of morphology and positive staining for CD1a and S-100 protein. Following the LCH-I protocol, he was randomized to receive high-dose methylprednisolone (30 mg/kg days 1-3) and etoposide (150 mg/m^2 days 1-3 q 21 days $\times$ 8). One month after the completion of this treatment the disease relapsed, causing lymphadenomegaly, massive hepatomegaly (5 cm below the costal margin), splenomegaly (6 cm), and cytopenia (hemoglobin 6.4 g/dL, platelets 29×10^9/L). Despite treatment with a combination of cyclosporine (12 mg/kg/day orally), prednisone (1.5 mg/kg/day orally), etoposide (150 mg/m^2 days 1-3 q 21 days) and vinblastine (6 mg/m^2 every other week), the disease progressed with fever, massive hepatosplenomegaly, transfusion dependent anemia, severe thrombocytopenia.

Eleven months after diagnosis the child underwent allogeneic BMT from his HLA-matched, 7-year-old sister, who was heterozygous for β-thalassemia. The conditioning regimen consisted of busulfan (3.5 mg/kg/day for 4 days), cyclophosphamide (60 mg/kg/day for 2 days), melphalan (140 mg/m^2). He received 6.4×10^8/kg mononucleated bone marrow cells. Cyclosporine (1 mg/kg/day c.i. days 1 to 24, then 12 mg/kg/day orally days 25-140) was given as prophylaxis against graft-versus-host disease. Cotrimoxazole (20 mg trimethoprim/kg/week orally) was given as prophylaxis for *Pneumocystis carinii* pneumonia.

On day +24 marrow reconstitution was evident, with WBC 2.3×10^9/L, neutrophils $>0.5\times10^9$/L, and platelets 72×10^9/L. Engraftment was demonstrated by PCR DNA analysis. The patient was discharged on day 25. After transplantation he experienced fever for 11 days and developed signs of grade I cutaneous and intestinal graft-versus-host disease, that was treated with methylprednisolone from day 11 to day 68 (1 mg/kg/day for 18 days, then tapered). He became transfusion independent on day 24; the hemoglobin value was 7.5 g/dL on day 54 and has remained > 10 g/dL since day 200. Features of heterozygous β-thalassemia have

Table 1. Summary of seven patients with LCH who underwent bone marrow transplantation.

Source	*Sex/Age (years)*	*Donor*	*Duration of LCH*	*Previous treatment*	*Organs involved*	*Conditioning regimen*	*GVHD prophylaxis*	*Reactivation*	*Survival months*	*Outcome*
Ringden	M/20	sister	9 y	RT, surgery, VBL, MTX, VCR, CHL, PDN, CY; MOPP; ARAC, VP16	lymph nodes, liver, lung, bone	CY 120 mg/kg, melphalan 90 mg/m^2, IT-MTX; TBI 200cGyx4	CSA; itMTX *	no	30+	Alive and well
Stoll	M/18	brother	3 y	PDN, CY, VCR; RT; 6-MP	lymph nodes, liver, lung, bone, GI, CNS	CY 200 mg/kg TBI 200 cGyx6	CSA, MTX	no	112+	Alive and well; hypergonadotropic hypogonadism
Greinix 952	M/29	brother	4 m	CHOP, SPL	lymph nodes, liver, lung, pleura, BM	CY, BCNU, TBI 1000 cGy	MTX	yes	11	Died of LCH
Greinix 5187	F/1.5	sister	7 m	VBL, PDN, 6-MP, CHL, SPL RT,	lymph nodes, spleen, liver, lung, bones, BM, skin	CY, TBI 1350 cGy	MTX	no	70+	Alive and well; on GH therapy
Greinix 1323	F/15	–	11 m	CHOP, BLEO, SPL	lymph nodes, liver, lung, skin	CY, TBI 1575 cGy	–	yes	<1	Died of LCH
Greinix 3895	F/45	–	5.5 y	MACOP-B, CY, ADR, ARAC, VP16	lymph nodes, spleen, liver, lung	CY, TBI 1200 cGy	–	no	96+	Alive and well
Present case	M/3	sister	11 m	PDN, VP16, CSA, VBL	lymph nodes, spleen, liver, lung, BM, skin	busulphan 14 mg/kg, CY 120 mg/kg, melphalan 140 mg/m^2	CSA	no	25+	Alive and well

*M = HLA matched; RT = radiotherapy; VBL = vinblastine; MTX = methotrexate; VCR = vincristine; CHL = chlorambucil; PDN = prednisone; CY = cyclophosphamide; MOPP = mechlorethamine+VCR+procarbazine+PDN; ARAC = cytarabine; VP16 = etoposide; it = intrathecal; *given on day 32 and every other week until day 102; TBI = total body irradiation; 6-MP = 6-mercaptopurine; CSA = cyclosporin-A; CNS = central nervous system; CHOP = cyclophosphamide + doxorubicin + vincristine + prednisone; SPL = splenectomy; ADR = adriamycin; BM = bone marrow; GH = growth hormone.*

been evident since then. Bone marrow aspirate was normal on days 25 and 94. At the time of this writing he remains in excellent condition, disease and treatment free, 25 months after transplantation.

Discussion

BMT has been used for the treatment of severe LCH in six cases (Table 1). The first case reported by Ringden *et al.* in 1987 (a 19-year-old patient with *fulminant* LCH) raised a debate about the suitability of BMT for this *non-malignant* disorder.[7] Three years later the Hannover group described an 18-year-old male who, 3 years after diagnosis of LCH, underwent BMT from his HLA-matched sib and still remains alive and disease free more than 9 years after BMT (ref. #8, and Riehm, personal communication, January 1996). Furthermore, in 1992 the Seattle group reported four patients treated with allogeneic (n=2) or autologous (n=2) BMT. Two of them were alive and disease free, one after allogeneic BMT.[9] The follow-up of those two patients could be extended thanks to the courtesy of Dr. R. Storb (personal communication, November 1995); the first patient is alive and well, with no signs of GVHD nor of LCH, 5.8 years after allogeneic BMT, and the other patient is also doing well 8 years after autologous BMT.

In summary, of the five patients (including the present case) who underwent BMT from a matched familial donor, four remained alive and well after 30+ to 112+ months. In the only observed failure, due to recurrent disease, survival was 11 months. No significant difference in the BMT conditioning regimen could be identified in these cases.

Autologous marrow rescue has been considered a less attractive option due to the inherent tendency of the marrow to give rise to LCH. Nevertheless, one of the only two cases reported showed disease- and treatment-free survival of over 8 years. Thus this opportunity can be considered as a second choice for patients who have no acceptable donor.

Disease status and activity are crucial to correct assessment of the prognosis and thus the possible indication for BMT in these patients. Although BMT for non-malignant hematologic disorders is indicated when the clinical course is very severe, it has been suggested that the advanced state of the disease and the complications coming from the disease itself, as well as from its treatment, may greatly reduce the chance of cure by BMT.

We decided to address the patient to early BMT from a familial donor since the disease was clearly refractory to chemotherapy and immunotherapy. In an ongoing therapeutic study by the Histiocyte Society (LCH-I-S), allogeneic BMT from an HLA matched familial donor is recommended for patients who fail to respond after six weeks of chemotherapy and fail to improve under immunotherapy. Since patient stratification at diagnosis does not seem to be fully satisfactory for identifying patients at the highest risk of LCH-related mortality, large trials are necessary to establish the criteria that will provide a definite diagnosis of refractory disease at the earliest point possible. In those cases, BMT seems to be a reasonable choice with the potential to cure, if an acceptable donor is available.[10]

In the present case the conditioning regimen did not include total body irradiation. This is different from what was previously reported by other groups, but is otherwise in keeping with recent reports of successful chemotherapy-only preparative regimens for another histiocytic disorder of childhood, i.e. hemophagocytic lymphohistiocytosis.[11]

Recent improvements in the selection of matched unrelated donors may increase the number of patients who might profit from BMT for refractory LCH. Nevertheless, some patients may lack an acceptable donor. The role of autologous marrow rescue still needs to be clarified. It is possible that the potent immune suppression provided by the conditioning regimen may prove to be effective in depressing the immune-mediated pathogenic mechanisms of LCH. Although this may not be supported by the only successful case report available, there is additional evidence that patients with histiocytosis or myelodysplasia with autologous reconstitution following allogeneic marrow transplant

may show prolonged remission even in the absence of any documentable chimerism (ref. #12; M. Aricò and V. Conter, unpublished data).

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