Allogeneic non-myeloablative stem cell transplantation for the patients with heavily pre-treated refractory lymphoma

We performed allogeneic non-myeloablative stem cell transplantation (allo-NST) in seven patients with heavily pre-treated refractory lymphoma. Two patients achieved unmaintained complete remission of short duration. Six patients died with progressive disease (n=2), graft-versus-host disease (n=2), pneumonia (n=1), or intracranial hemorrhage (n=1). This study showed high transplant-related mortality and inadequate control of lymphoma after allo-NST.

In patients with refractory lymphoma, allogeneic stem cell transplantation has a curative potential, which is mediated in part by graft-versus-lymphoma (GVL) effects.[1-4] The decreased risk of transplant-related complications associated with allogeneic non-myeloablative stem cell transplantation (allo-NST) may expand the eligibility of transplant candidates.[5-7] Several investigators have reported promising results of allo-NST in patients with lymphoma.[8-10] We performed allo-NST in seven patients with lymphoma which was refractory to multiple regimens of combination chemotherapy.

The conditioning regimen consisted of busulfan (4 mg/kg/day p.o. on days -7 and -6), fludarabine (30 mg/m^2/day i.v. on days -7 to -2), anti-thymocyte globulin (20 mg/kg/day i.v. on days -5 to -2), and methylprednisolone (2 mg/kg/day i.v. on days -5 to -2). Granulocyte colony-stimulating factor-mobilized peripheral blood stem cells from donors were infused on days 0 and 1. Cyclosporine was given starting on day -1 through day 60. The status of hematopoietic chimerism was evaluated using polymerase chain reaction (PCR) amplification of short tandem repeats or amelogenin loci at monthly intervals for 6 months.

Six patients had non-Hodgkin's lymphoma (NHL) and one had Hodgkin's disease (HD). All seven patients were heavily pre-treated and refractory to chemotherapy (Table 1). Of the six patients with NHL, five had bone marrow involvement and one had extensive bowel involvement. The patient with HD had disseminated disease involving the lung, liver, spleen, and lymph nodes. The patients had all received multiple courses of chemotherapy (median 3 regimens, range 2-4). No patient had had prior autologous stem cell transplantation.

All patients achieved an absolute neutrophil count over 500/μL at a median of day 11 (Table 2). Two of five patients who were evaluable for hematopoietic chimerism analysis on day 30 showed mixed chimerism. On day 60, only one of four evaluable patients showed mixed chimerism. Acute graft-versus-host disease (GvHD) was observed in four patients. Two patients progressed from acute to extensive chronic GvHD. Two patients achieved complete remission, one on day 21 and the other on day 92. These remissions were, however, short (44 and 48 days, respectively). The patient with HD showed partial remission after allo-NST, but he died of GvHD on day 121. Six patients died. Causes of deaths were progressive disease (n=2), GvHD (n=2), pneumonia (n=1), or intracranial hemorrhage (n=1). Only one patient is alive with relapsed disease at 457 days after allo-NST.

Our study showed high transplant-related mortality and inadequate control of lymphoma after allo-NST in this group of heavily pre-treated refractory patients with large tumor burden. GVL effects depend on at least partial reconstitution of immunity and generally require weeks to months to develop after transplantation.[2] In patients with progressive refractory lymphoma, there is little time to exploit potentially beneficial GVL effects.[5,6] Chemotherapeutic agents used as the conditioning regimen in our study have relatively little anti-lymphoma activity. The use of a less intensive conditioning regimen with anti-lymphoma effects may make it possible to achieve disease remission and stable engraftment with acceptable toxicity.[9] Optimal methods for GvHD prophylaxis should also be investigated in the setting of allo-NST.

Table 1. Pre-transplant patient characteristics.

UPN	Age/Sex	Dx	Time to BMT from Dx (days)	No. previous chemotherapy regimens (previous regimens)	Prior RT	Stage at allo-NST (sites of involvement)	Status at allo-NST
138	25/M	NHL (MCL)	885	4 (CHOP, MINE, MTX/6-MP, VPDL)	No	IVB (BM, cervical LN)	Refractory relapse
143	35/M	NHL (PTL)	114	3 (ProMACE/CytaBOM, COBEM, CEDBM)	No	IVB (BM, tonsil, cervical LN)	Primary refractory disease
146	27/M	NHL (LBL)	273	4 (VPDL, VM26/araC, CODOX-M, ProMACE/CytaBOM)	Yes	IVB (BM, CNS, mediastinal LN)	Refractory relapse
161	48/M	NHL (NK/T)	101	3 (CHOP, COBEM, CEDBM)	No	IVB (jejunum, colon)	Primary refractory disease
162	56/M	NHL (PTL)	213	3 (COBEM, CEDBM, CHOP)	No	IVB (BM, cervical & axillary LN)	Untreated relapse with short remission duration
168	53/M	HD (NS)	570	4 (ABVD, COPP, EDAP, EPOCH)	Yes	IVB (lung, liver, spleen, cervical LN)	Refractory relapse
171	22/F	NHL (MCL)	206	2 (CHOP, DHAP)	No	IVB (BM, axillary & intra-abdominal LN)	Primary refractory disease

UPN= unique patient number; Dx = diagnosis; NHL = non-Hodgkin's lymphoma; HD = Hodgkin's disease; MCL = mantle cell lymphoma; PTL = peripheral T cell lymphoma; LBL = lymphoblastic lymphoma; NK/T = NK/T cell lymphoma; NS = nodular sclerosis; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisolone; MTX = methotrexate; 6-MP = 6-mercaptopurine; VPDL = vincristine, prednisolone, doxorubicin, L-asparaginase; ProMACE/CytaBOM = prednisolone, doxorubicin, cyclophosphamide, etoposide, cytarabine, bleomycin, vincristine, methotrexate; COBEM = cyclophosphamide, etoposide, vincristine, bleomycin, methotrexate, prednisolone; CEDBM = cyclophophamide, etoposide, doxorubicin, bleomycin, methotrexate; VM26/araC = teniposide, cytarabine; CODOX-M = cyclophosphamide, vincristine, doxorubicin, methotrexate, cytarabine; ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; COPP = cyclophosphamide, vincristine, procarbazine, prednisolone; EDAP = etoposide, dexamethasone, cisplatin, cytarabine; EPOCH = etoposide, vincristine, doxorubicin, cyclophosphamide, prednisolone; DHAP = dexamethasone, cytarabine, cisplatin; RT = radiotherapy; allo-NST = allogeneic non-myeloablative stem cell transplantation; BM = bone marrow; LN = lymph node; CNS = central nervous system.

Table 2. Post-transplant outcomes.

UPN	Engraftment		Chimerism (% recipient cells)		GVHD		CMV infection	Post-transplant course
	ANC > 500/μL	PLT > 20×10³/μL	Day 30	Day 60	Acute	Chronic		
138	day 11	day 12	MC (20%)	MC (40%)	Grade I (skin)	-	Yes	CR (day 21); Relapse (day 65; BM, bone); Died of disease (day 277)
143	day 12	day 17	MC (19%)	CC	Grade II (skin)	Extensive (skin, mouth, eye, liver)	No	CR (day 92); Relapse (day 140; tonsil); Alive with disease (day 457+)
146	day 11	day 20	CC	CC	No	-	Yes	Persistent (BM, CNS); Died of disease (day 70)
161	day 10	-	-	-	No	-	No	Died of ICH (day 15)
162	day 11	-	CC	-	No	-	No	Died of pneumonia (day 49)
168	day 10	day 14	CC	CC	Grade IV (skin)	Extensive (skin, GI)	Yes	PR (day 91); Died of chronic GVHD (day 121)
171	day 10	-	-	-	Grade IV (skin, GI, liver)	-	No	Died of acute GVHD (day 11)

UPN= unique patient number; ANC = absolute neutrophil count; PLT = platelet count; MC = mixed chimerism; CC = complete chimerism; GVHD = graft-versus-host disease; GI = gastrointestine; CMV = cytomegalovirus; CR = complete remission; BM = bone marrow; CNS = central nervous system; ICH = intracranial hemorrhage.

Our results in patients with heavily pre-treated refractory lymphoma are discouraging. For these patients, alternative strategies must be explored to improve disease control.

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