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Haematopoietic stem cell transplantation for refractory autoimmune cytopenia

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Summary

This study describes the outcome of patients receiving haematopoietic stem cell transplantation (HSCT) to treat severe refractory autoimmune cytopenia. The registry of the European Group of Blood and Marrow Transplantation holds data on 36 patients receiving 38 transplants, the first transplant was autologous for 27 and allogeneic for nine patients. Patients had autoimmune haemolytic anaemia (autologous: 5; allogeneic: 2), Evans's syndrome (autologous: 2; allogeneic: 5); immune thrombocytopenia (autologous: 12), pure red cell aplasia (autologous: 4; allogeneic: 1), pure white cell aplasia (autologous: 1; allogeneic 1), or thrombotic thrombocytopenic purpura (autologous: 3). Patients had longstanding disease having failed multiple prior treatments. Among 26 evaluable patients mobilized for autologous HSCT, three died of treatment-related causes, one died of disease progression, seven were non-responders, six patients had transient responses and nine had continuous partial or complete remission. Of the seven evaluable patients receiving allogeneic HSCT, one died of treatment-related complications, one with transient response died of progressive disease and five had a continuous response. Autologous and allogeneic HSCT may induce a response in a subset of patients with autoimmune cytopenia of long duration albeit at the price of considerable toxicity.

Keywords: autoimmune cytopenia, immune thrombocytopenia, Evans's syndrome, pure red cell aplasia, autologous, allogeneic, stem cell transplantation.

Autoimmune diseases represent a heterogeneous group of disorders with genetic, environmental and individual aetiological factors. Immunosuppression and immunomodulation are therapeutic strategies. Corticosteroids and other immunosuppressive agents are often used successfully. There are patients, however, who do not respond and require more intensive treatment (Bussel, 2000; Davidson & Diamond, 2001; McMillan, 2001; Portielje *et al*, 2001; Cines & Blanchette, 2002).

The observation in some patients with concomitant autoimmune diseases receiving haematopoetic stem cell transplantation (HSCT) to treat malignancy, animal models using HSCT to prevent and treat severe autoimmune diseases, and theoretical considerations suggest that intensive immunoablation followed by haematopoietic stem cell rescue may improve severe autoimmune disease (Van Bekkum, 2000; Ikehara, 2001). Furthermore, allogeneic HSCT may be viewed as an attempt to cure autoimmune disease by replacing the immune system (Slavin *et al*, 2000; Oyama *et al*, 2001; Marmont *et al*, 2003).

Since 1995, HSCT, mainly autologous, has been explored to treat a variety of autoimmune diseases in collaborative studies (Tyndall *et al*, 1999). These included multiple sclerosis (Fassas *et al*, 2002), scleroderma (Binks *et al*, 2001), lupus (Traynor *et al*, 2000; Jayne *et al*, 2004), rheumatoid arthritis (Snowden *et al*, 2004) and other diseases with variable success; phase III studies are currently underway. Autoimmune haematological cytopenias, such as immune thrombocytopenia (ITP), autoimmune haemolytic anaemia (AIHA), the combination of both (Evans's syndrome), pure red cell aplasia (PRCA) and possibly also thrombotic thrombocytopenic purpura (TTP) may also be amenable to high-dose treatment followed by stem cell replacement. This report summarizes the outcome of patients reported to the European Group of Blood and Marrow Transplantation (EBMT).

Patients and methods

Patients

Thirty-six patients with refractory autoimmune cytopenia, receiving autologous or allogeneic HSCT to modify the course of the disease and reported to the registry of the autoimmune disease working party of the EBMT, were included in this study. Patients were followed for at least 3 months post-transplant. Patient and disease characteristics are shown in Table I. These 36 patients had received 38 transplants, one patient had undergone mobilization for autologous transplant without receiving a transplant, following a complete response, three patients had undergone a second allogeneic HSCT after having failed autologous HSCT. Transplants were autologous for 26 and allogeneic for nine patients. Patients had AIHA (autologous: 5; allogeneic: 2), Evans's syndrome (autologous: 2; allogeneic: 5); ITP (autologous: 12), PRCA (autologous: 4; allogeneic: 1), pure white cell aplasia (PWCA) (autologous: 1; allogeneic: 1) and TTP (autologous: 3). There were important differences among patients selected for autologous and allogeneic HSCT. The recipients of autologous transplants were older (median age: 31 years; range, 4–48 years) than recipients of allogeneic HSCT (median: 14 years; 2–57 years) and had disease of longer duration 83 (3–299) months *versus* 16 (2–119) months. Nearly all patients had undergone and failed multiple treatments.

Data collection

All patients transplanted between 1997 and 2002 for autoimmune cytopenia were identified through the EBMT registry. Information on some of the patients' and disease characteristics, and the post-transplant course was available through the registry. Additional information, especially on blood counts was sought through more extensive forms. We were able to obtain this information on 33 of 36 patients. Because these are rare transplants we included all 36 patients in the study.

Transplants

Details of the transplantation procedure are given in Table I. The stem cell source was mobilized peripheral blood in the majority of recipients of autologous transplants (24/27) but mainly bone marrow in allotransplant recipients (6/9). In recipients of autotransplants, blood stem cells were mobilized with cyclophosphamide + granulocyte colony-stimulating factor (G-CSF) in 13 cases, G-CSF alone in eight and other regimens in two.

Donors for allotransplant recipients were human leucocyte antigen-identical siblings in six cases, unrelated donors in two and a haploidentical parent in one.

The grafts were T-cell depleted in 20 of 26 recipients of autotransplants and in one of seven allotransplant recipients. Conditioning regimens used were heterogeneous as shown in Table I. Reduced intensity conditioning regimens were used in four of nine allotransplant recipients.

Outcomes

Peripheral blood counts were collected at 1, 3, 6, 12 months post-transplant and yearly thereafter. Complete remission was defined as normalization of blood counts [haemoglobin (Hb) >12 g/dl, neutrophils $>1{\cdot}5 \times 10^9$/l, platelets $>150 \times 10^9$/l]; partial remission was an improvement to levels above 8 g/dl for Hb, 50×10^9/l for platelets and $0{\cdot}5 \times 10^9$/l for neutrophils. Progression-free survival (PFS) was defined as the probability of being alive without disease progression. Mortality was defined as death due to any cause. Treatment-related mortality (TRM) was defined as death without disease progression. Because of the difficulty in assessing whether death due to haemorrhagic complications in patients with thrombocytopenia should be attributed to the underlying disease or to treatment, these deaths were counted as TRM. Immune reconstitution was assessed by $CD4^+$ cell counts.

Table I. Patient and disease characteristics.

	Autologous	Allogeneic
Disease		
AIHA	5	2
Evans's syndrome	2	5
ITP	12	–
PRCA	4	1
PWCA	1	1
TTP	3	–
Sex M/F	12/15	7/2
Age, years, median (range)	31 (4–48)	14 (2–57)
Disease duration, months, median (range)	83 (3–299)	16 (2–119)
Follow-up, months, median (range)	43 (3–84)	41 (7–76)
Prior treatment (*n*/*n* evaluable)		
Splenectomy	15/25	3/6
Steroids	24/25	5/6
Azathioprin	8/25	1/5
Intravenous immunoglobulins	17/24	5/6
Cyclophosphamide	21/25	2/6
Ciclosporin	14/25	3/6
ATG	6/25	1/6
Number of previous lines of treatment		
2–5	14	3
6–11	10	2
Stem cell source		
Bone marrow	3	6
Peripheral blood	24	3
Mobilization		
G-CSF	8	
Cyclophosphamide + G-CSF	13	
Other	2	
Donor		
HLA-identical sibling		6
Matched unrelated donor		2
Haploidentical parent		1
Female donor into male recipient *versus* other donor–recipient sex combinations		2/5
Conditioning		
BEAM ± ATG	2	
Cy	4	
Cy + thiotepa	1	2
Cy ± ATG ± other drugs	12	3
Cy + radiation ± other drugs	2	1
BuCy ± ATG		2
Melphalan	2	
Fludarabine + other	2	
Purging/cellular engineering		
None	6	6
CD34 + selection	12	1
CD34 + selection/T-cell depletion	4	
T-cell depletion	1	
Chemotherapy	1	

AIHA, autoimmune haemolytic anaemia; ITP, immune thrombopenia; PRCA, pure red cell aplasia; PWCA, pure white cell aplasia; TTP, thrombotic thrombocytopenic purpura; ATG, antithymocyte globulin; G-CSF, granulocyte colony-stimulating factor; HLA, human leucocyte antigen; BEAM, BCNU (carmustine), etoposide, cytarabine, melphalan; Cy, cyclophosphamide; BuCy, busulphan + cyclophosphamide.

Statistical analysis

Median and range of values analysed are given where appropriate. The Kaplan–Meier estimator was used to assess PFS, and overall survival. Results are given as probabilities ±95% confidence interval. Patients undergoing second transplants were censored at the time of second transplant.

Results

Toxicities of the procedure, proportion of patients with neutropenic fever, transfusion requirements, time to neutrophil recovery and proportion of patients with late events and TRM are shown in Table II. Three of the 26 recipients of autologous transplants died of treatment-related complications (one patient with ITP died of cerebral haemorrhage, one patient with ITP and AIHA each died of septicaemia). Among the recipients of allogeneic transplants, one patient with Evans's syndrome died of treatment-related complications (interstitial pneumonitis and haemorrhage).

Table III shows data on outcome by disease and type of transplantation. Of the 27 patients mobilized for autologous transplants eight patients showed no evidence of response, one with AIHA died of progressive disease, three died of treatment-related complications, six had a transient response and nine had a continuous response after transplantation. One patient was not evaluable for response (data unavailable).

Among recipients of allogeneic transplants, one had a transient response and five had a continuous response (the patient with a transient response later died of progressive Evans's syndrome) and one patient died of transplant-related complications. Two patients were alive without disease progression but detailed response data were not available.

Table II. Toxicity.

	Autologous	Allogeneic
WHO III/IV toxicity during mobilization (*n*/*n* evaluable)	2/24	
WHO III/IV toxicity during transplantation (*n*/*n* evaluable)	4/25	1/6
Neutropenic fever during transplantation	14/25	3/6
Platelet transfusion requirement (units)		
0–5	16	4
>5	8	2
Time to neutrophil recovery (ANC > $0{\cdot}5 \times 10^9$/l), median (range)	10 (0–44)	13·5 (10–110)
Treatment-related death	3	1
Late events		
Chronic GvHD (*n*/*n* evaluable)	–	2/6
Death due to disease progression	1	1

WHO, World Health Organization; ANC, absolute neutrophil count; GvHD, graft *versus* host disease.

Table III. Outcome by disease.

Disease	Autologous	Allogeneic
AIHA	$n = 5$	$n = 2$
	Death, TRM (1)	Continuous remission (2)
	Death, progressive disease (1)	
	No response (2)	
	Transient response (1)	
Evans's syndrome	$n = 2$	$n = 5$
	Transient response (1)	Death, TRM (1)
	Continuous remission (1)	Death, progressive disease (1)
		Not evaluated (2)
		Continuous remission (1)
ITP	$n = 12$	
	Death, TRM (2)	
	Not evaluated (1)	
	No response (3)	
	Transient response (2)	
	Continuous remission (4)	
PRCA	$n = 4$	$n = 1$
	No response (2)	Continuous remission (1)
	Transient response (2)	
PWCA	$n = 1$	$n = 1$
	Continuous remission (1)	Continuous remission (1)
TTP	$n = 3$	
	Continuous remission (3)	

AIHA, autoimmune haemolytic anaemia; ITP, immune thrombopenia; PRCA, pure red cell aplasia; PWCA, pure white cell aplasia; TTP, thrombotic thrombocytopenic purpura; TRM, treatment-related mortality.

Interestingly, the PRCA patient who received allogeneic HSCT is in continuous complete remission with autologous reconstitution. One ITP patient had a complete and continuous response to chemotherapy given to mobilize peripheral blood stem cells and chose not to undergo transplantation.

Three patients who did not respond or who relapsed after autologous HSCT underwent an allogeneic HSCT. One patient with AIHA was in continuous complete remission 4 years after a transplant from an unrelated donor, one patient with PRCA underwent successful allogeneic transplantation from a matched sibling and one patient with AIHA died of veno-occlusive disease of the liver after an unrelated donor transplant. Figure 1 shows the platelet counts in nine patients with ITP undergoing autologous HSCT (Fig 1A), Hb concentration in three patients that underwent allogeneic HSCT for AIHA (Fig 1B) and Hb concentration and platelet counts in three patients with TTP after autologous HSCT (Fig 1C). Figure 2 shows $CD4^+$ cell counts in patients undergoing autologous HSCT. The reconstitution of $CD4^+$ lymphocytes was slow in these patients. Figure 3 shows the overall survival and PFS in recipients of autologous and allogeneic HSCT. Overall survival probabilities in autotransplant recipients were $84 \pm 15\%$, and $78 \pm 28\%$ in allotransplant recipients at 5 years. PFS probabilities in autotransplant recipients were $45 \pm 21\%$, and $78 \pm 28\%$ in allotransplant recipients.

Discussion

This is a descriptive study of patients reported to the EBMT registry undergoing autologous or allogeneic HSCT for autoimmune cytopenia. Patients suffered from AIHA, ITP, Evans's syndrome, PRCA, PWCA and TTP. Patients with cytopenia due to systemic lupus erythematosus were not included here and have been reported separately (Jayne *et al*, 2004).

Although sharing a similar procedural technology, autologous and allogeneic HSCT differ significantly with respect to their immunological consequences. Allogeneic HSCT is associated with more profound immunosuppression and graft *versus* host disease, which may mimic some clinical aspects of autoimmune disease.

In this study, autologous HSCT led to a sustained response in a significant minority of patients (9/26; four ITP, one Evans's syndrome, three TTP, one PWCA). The associated toxicity was considerable: three patients died of transplant-related complications, one ITP patient of cerebral bleeding, two patients of infectious complications. This rather high toxicity rate may be explained by long disease duration in patients having failed multiple treatments, as exemplified by two non-responsive patients dying of uncontrollable AIHA. Apart from these deaths, toxicities appeared manageable.

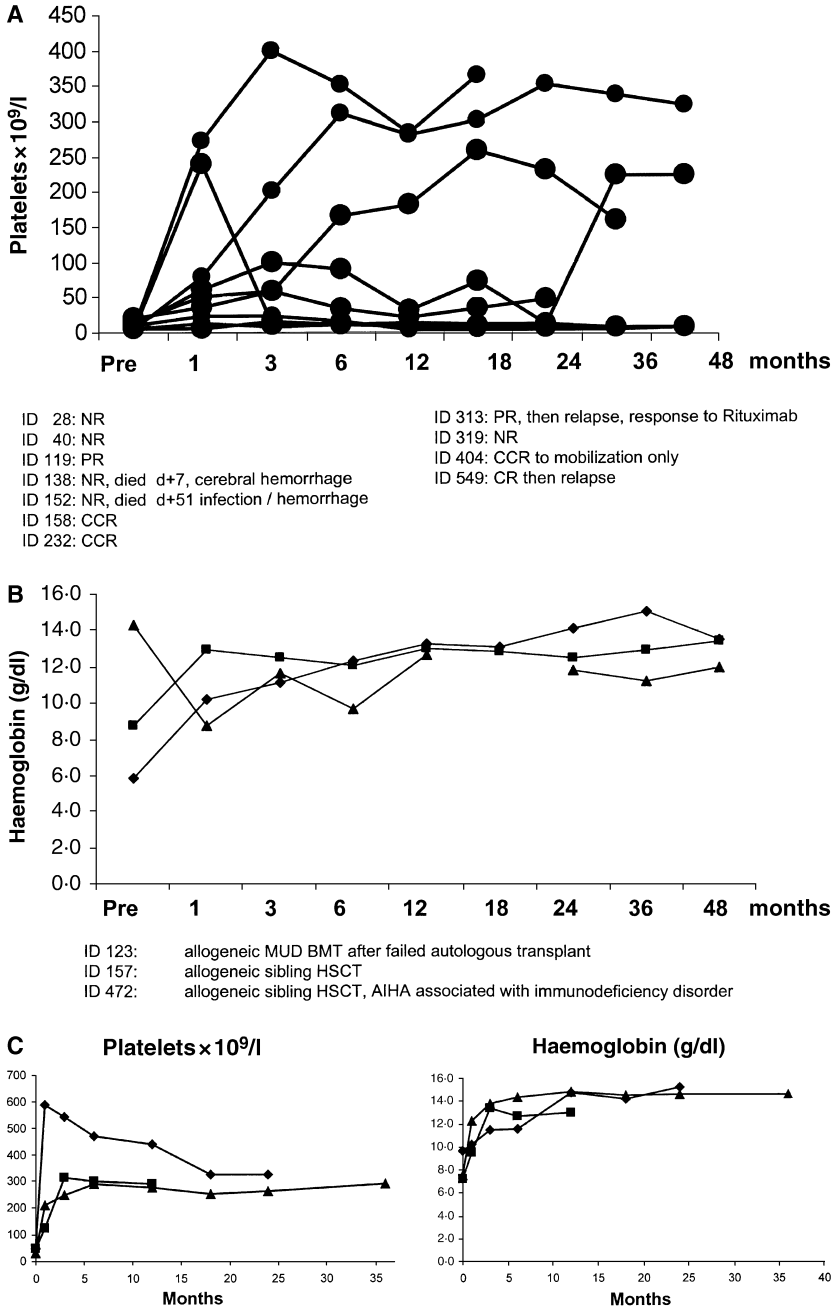

Fig 1. (A) Platelet counts in nine patients with immune thrombocytopenia (ITP) undergoing autologous haematopoietic stem cell transplantation (HSCT). One patient had a relapse after a partial remission (PR) and responded to rituximab. NR, no response; CCR, continuous complete remission; CR, complete remission. (B) AIHA: Hb concentration in three patients with successful allogeneic transplantation. One patient had a normal Hb prior to treatment due to a response to high-dose steroids. MUD BMT, matched unrelated donor bone marrow transplant. (C) thrombotic thrombocytopenic purpura (TTP), platelets and Hb in three patients after autologous transplantation.

Neutropenic fever was common and transfusion requirements were not more than expected for such a transplant population. Allogeneic HSCT might achieve a higher response rate, five of seven patients showed a sustained response: two AIHA, one Evans's syndrome, one PRCA, one PWCA.

With regard to the procedure toxicity, one patient (Evans's syndrome), who received a haploidentical transplant, died of complications. One patient (also with Evans's syndrome) died of progressive disease. In this study, the patients selected for allogeneic HSCT were younger and had a shorter disease duration and less pretreatment, reflecting the general tendency to select young patients with severe disease for allogeneic transplantation. Only a few allogeneic HSCT have been performed for autoimmune disorders in general and the majority of these were in children and young adults with autoimmune cytopenia. For these patients, the heterogeneity of regimens used and of donors available precludes any meaningful analysis of predictive factors.

There is limited information on HSCT in autoimmune cytopenia in the medical literature. In a phase II study by the National Institutes of Health (NIH) that included 14 patients (nine with ITP and five with Evans's syndrome), autologous HSCT was well tolerated with no early TRM (Huhn *et al*, 2003). Two patients died, one of myeloma and one due to

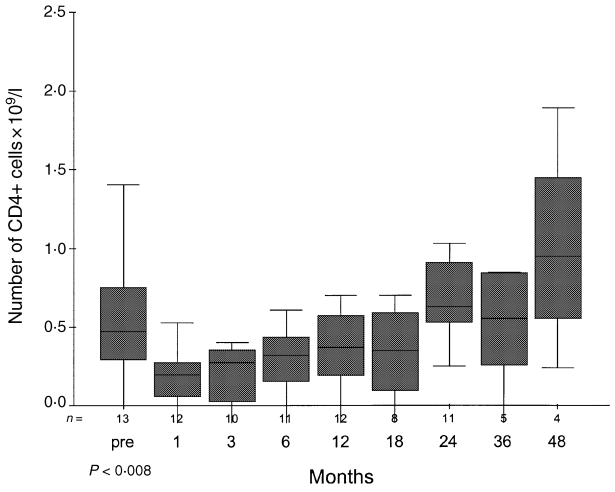

Fig 2. CD4-lymphocytes after autologous transplantation for haematological cytopenia.

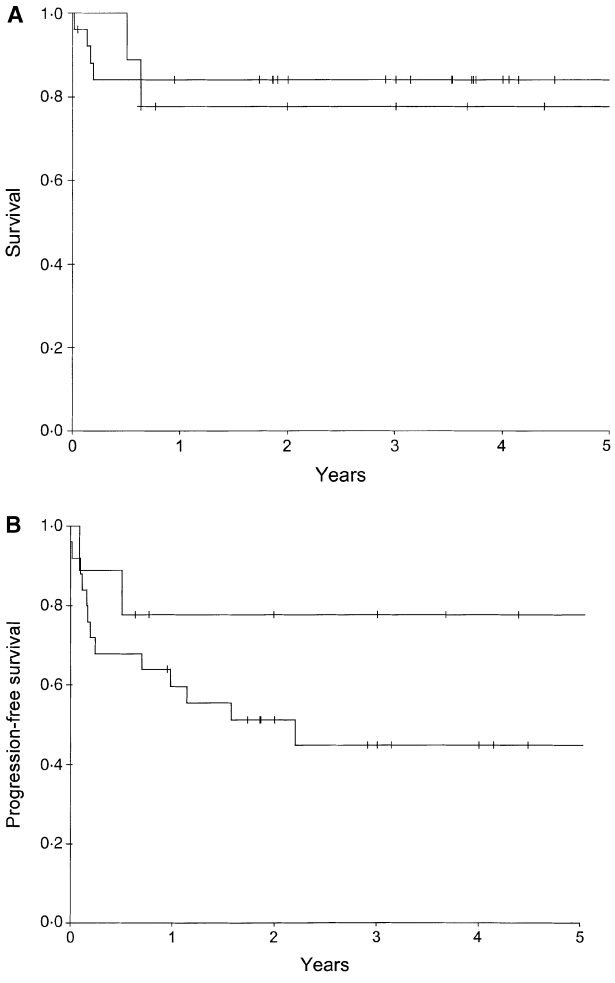

Fig 3. (A) Overall survival in recipients of an autologous transplant: 84 ± 15%, in recipients of an allogeneic transplant: 78 ± 28%. (B) Progression-free survival in recipients of an autologous transplant: 45 ± 21%, in recipients an allogeneic transplant: 78 ± 28%.

complications of an intravenous line infection. The overall response rate was 57% (43% complete response, 14% partial response). There were no late relapses. The patient population in this study was, as in the present analysis, heavily pretreated. Results in the NIH study appear more favourable, possibly due to the influence of patient selection in a single centre phase II study. Other reports of single cases [Lim *et al*, 1997; Skoda *et al*, 1997; Marmont *et al*, 1998; Seeliger *et al*, 2001 (included also in this report)] showed either transient or no response to the treatment. Some patients with concomitant autoimmune cytopenia were transplanted for malignancy and showed a response (Demirer *et al*, 1999; Jindra *et al*, 1999). One of the allotransplant recipients from this study has also been reported in elsewhere (Marmont *et al*, 2003).

The present study has several limitations. The patient number is small and the data are incomplete as we were not able to obtain detailed data on all patients. We nevertheless felt that, given the rare use of HSCT technology for autoimmune cytopenia, we should present the patients as completely as possible (Gratwohl *et al*, 2001). Treatment protocols, mobilization and conditioning regimens were heterogeneous and the small patient number precludes any analysis of these factors. As this is a registry study, we did not have data on anti-platelet and anti-red cell antibodies. These data represent the almost total European experience of HSCT technology for autoimmune cytopenia and suggest that autologous and allogeneic HSCT may induce response in a subset of patients with severe autoimmune cytopenia of long duration, albeit at the price of considerable toxicity. Further phase II studies should be carried out using careful patient selection and uniform treatment regimens.

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