CONCISE REPORT

Bone Marrow Transplantation in Multiple Myeloma: Report From the European Cooperative Group for Bone Marrow Transplantation

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Of 14 patients who received an allogeneic bone marrow graft from HLA-compatible sibling donors, 10 have survived for 6 to 34 months posttransplantation (median, 12 months). Four patients have died, two of relapse at extramedullary sites, one of severe acute GVHD, and one from GI bleeding and pericardial effusion. One patient is alive in relapse and four patients have signs of minimal persistent disease. Five patients are well without signs of active disease. Minor improvement in osteolytic lesions on X-ray were seen in three patients, but the X-ray bone structure was mainly unchanged in most patients. Bone marrow transplantation appears promising for treatment of certain patients with multiple myeloma.

ALLOGENEIC BONE MARROW transplantation (BMT) has proved to be an efficient method for treatment of patients with a variety of hematological malignancies, in particular acute leukemia and chronic myelocytic leukemia.[1] BMT has also been performed in a few patients with multiple myeloma,[2-6] three of whom have survived more than two years posttransplantation, although they were transplanted in an advanced stage of the disease. Within the European Cooperative Group for Bone Marrow Transplantation (EBMT), 14 myeloma patients have been transplanted. This report describes the outcome for these 14 patients, some of whom have been presented previously in preliminary reports.[5-6]

MATERIALS AND METHODS

Fourteen patients (8 women, 6 men, median age 35 years) (Table 1) were reported to the EBMT registry, having been transplanted for multiple myeloma. All patients had been treated with cytotoxic drugs prior to BMT. Five were in stage III, two in stage II, and seven in stage I prior to the start of consolidation treatment. Five were considered refractory to treatment (patients 4, 6, 7, 8, and 10), while 9 were not refractory to first- or second-line treatment. Five patients had received only melphalan and prednisolone before transplant; two of them were refractory to this treatment, and two were responding. Nine patients had received a combination of various cytotoxic drugs. The time from diagnosis to BMT varied considerably (median 14 months).

All patients were conditioned before BMT with both cyclophosphamide and total body irradiation (modified Seattle protocol).[7] Five patients received additional cytotoxic drugs, ie, CCNU (lomustine), BCNU (carmustine), vincristine, prednisolone, and melphalan in variable regimens. Eight patients received total body irradiation in a single dose and six in fractions over three to five days. The total dose varied between 9.5 and 12 Gy, according to whether it was given as a single dose or in fractions.

All patients were advised of BMT procedures and attendant risks, in accordance with institutional guidelines, and gave informed consent.

RESULTS

Of the 14 patients, 10 are alive 6 to 34 months (median 12 months) post-BMT (Table 1). Four patients died ½ to 4½ months posttransplant. One patient with an IgG-lambda plasma-cell leukemia died with a meningeal relapse 4½ months post-BMT, and one patient with an IgG-kappa myeloma died with a cerebral relapse. In these two patients there were no signs of generalized disease. One patient died from GI bleeding and pericardial effusion, and the fourth patient died of severe GVHD.

Among the surviving patients five were well and without signs of disease. Two of them were considered refractory to the chemotherapy before BMT. They had no abnormal serum immunoglobulins, light chains in the urine, or abnormal plasma cells in the marrow at reporting. Four patients had persistent minimal signs of disease (patients 3, 4, 10, and 14) (Table 1) and one patient relapsed (patient 5).

The pretransplant bone structure on X-ray was only moderately changed posttransplantation. Of the five patients without signs of active disease in serum, urine or bone marrow post-BMT, three had advanced lytic lesions before transplant. After BMT no clear change was observed in one of these patients, while two were rated as having only minor lytic lesions. In the other two patients no change in the bone structure was observed posttransplant (normal bone structure and minor bone lesions, respectively). Of the four patients with minimal disease, two were rated as having

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Table 1. Bone Marrow Transplantation in Multiple Myeloma

Patient	Sex/Age	Type of Myeloma	Treatment Before BMT	Time Diagnosis—BMT mo	Stage at BMT	Conditioning			Survival mo post-BMT	GVHD		Comments
						Chemo	TBI Total Dose	TBI No. of Days		Acute Grade	Chronic	
1	F /29	Plasma cell leukemia IgDλ	M, C+V+P+M+D	7	2	C 120 mg/kg CCNU 340 mg	12.0	3	4½	II	mild	Dead, meningeal relapse
2	F /45	IgGκ	M+P+D+A	18	1	C 120 mg/kg M 140 mg/m²	12.0	3	3½	0	0	Dead, cerebral relapse
3	F /35	IgAλ	C+P+CCNU+D	7	1	C 120 mg/kg	10.0	1	12+	0	0	Alive, well, minimal disease; persistent S-Ig <0.5 g/L; urinary light chains 0.2 g/L
4	M/35	IgAκ	V+D+C+P	6	2	C 120 mg/kg BCNU 3.5 mg/kg V 2 mg,P60 mg/kg	12.0	3	13½	0	0	Alive, well minimal disease; persistent S-Ig 5g/L
5	F /39	IgAλ	M+C+P	13	1	C 120 mg/kg M 140 mg/m²	11.0	5	11+	I	0	Alive, relapse
6*	M/32	BJκ	C+V+P+M	25	3	C 120 mg/kg	10.0	1	9+	I	0	Alive, well, no signs of active disease
7*	F /38	IgGλ	M+P	18	3	C 120 mg/kg	10.0	1	½	0	0	Dead, GI bleeding and pericardial effusion
8*	F /46	IgAκ	M+P	5½	3	C 120 mg/kg	10.0	1	34+	I	0	Alive, well, no signs of active disease
9	M/29	BJκ	M+P	8	3	C 120 mg/kg	10.0	3	12+	I	0	Alive, well, no signs of active disease
10	M/44	IgAλ	M+P	8	1	C 120 mg/kg M 4 mg/kg	10.0	1	8+	I	0	Alive, well, minimal disease 10% plasma cells in the bone marrow
11*	F /35	IgGκ	M+P	24	1	C 120 mg/kg	10.5	1	28+	I	mild	Alive, well, no signs of active disease
12*	M/44	IgAκ	M+P M+D+BCNU+C+V	16	3	C 120 mg/kg M 2 mg/kg BCNU 5.5 mg/kg	9.5	1	12+	I	mild	Alive, well, no signs of active disease
13*	M/34	IgAκ	M+P M+P+BCNU+C+V	58	1	C 120 mg/kg M 2 mg/kg BCNU 5.5 mg/kg	10.0	1	2	IV	0	Dead, severe acute GVHD
14	F /38	IgGκ	V+C+M+P V+D+P	14	1	C 120 mg/kg	12.0	3	6+	I	mild	Alive and well, minimal disease; persistent S-Ig 6 g/L

Abbreviations: M, melphalan; C, cyclophosphamide; V, vincristine; P, predniso(lo)ne (or dexamethasone); A, cytosine arabinoside (ARA-C); D, doxorubicin; CCNU, lomustine; BCNU, carmustine.
*Earlier reported after shorter follow-up time (5,6)

minor bone lesions before BMT. In one of these patients there was no change; the other had normal bone structure at reporting. Two patients had normal bone structure before transplant. In one there is still no change, while one now has minor bone lesions.

Only one patient had severe (grade IV) acute GVHD (patient 13). No patient had severe chronic GVHD, and four had mild chronic GVHD.

DISCUSSION

This report shows that bone marrow transplantation can be successful in patients with multiple myeloma. Five of 14 patients are well without signs of active disease 9 to 34 months posttransplantation. Four other patients are well with only minimal changes in either serum Ig, urinary light chains, or bone marrow plasma cells, indicating persistent disease. Although the observation time is short (median 12 months for surviving patients), only three patients have relapsed. The nature of minimal persistent disease is uncertain, and these patients may well relapse later. In fact, patient 5 had signs of persistent disease for some months before relapse at 11 months post-BMT. On the other hand, the four patients with persistent minimal disease at reporting have now survived for 6, 8, 12, and 13½ months without progressing. It is possible that these minimal changes may disappear, perhaps due to a graft-versus-myeloma effect as previously described for acute leukemia.[8] The significance of persistent bone lesions on X-ray is difficult to judge. Three of five patients who were well without signs of active disease at this report had advanced osteolytic lesions at transplant. Although one still has advanced osteolytic lesions and the other two minor ones, none has signs of active disease 9 to 12 months post-BMT. One patient who had minor osteolytic lesions unchanged post-transplant has now survived for 34 months. Thus, persistent osteolytic lesions may not indicate a risk for relapse.

Side effects of BMT in this material were in general not different from those described previously.[1] It is of interest to note, however, that only one patient had severe acute GVHD (T cell–depleted) and none had severe chronic GVHD. Thus, despite the relatively advanced age of the patients, GVHD was a minor problem.

The optimal time for transplantation of patients with multiple myeloma cannot be judged from the present report. However, it seems reasonable to transplant patients with an HLA-compatible sibling donor if the prognosis is poor with current chemotherapy. Recently some prognostic factors have been delineated,[9] ie, patients with a rapid response to treatment, with IgD myeloma, and with a high thymidine-incorporation labeling index appear to have a relatively poor prognosis. These patients could perhaps be transplanted at an early stage of the disease. Also, since two out of five patients considered refractory to chemotherapy were without signs of active disease 9 and 34 months post-BMT, patients that are resistant to first-line treatment may well be successfully transplanted before second-line treatment is instituted.

APPENDIX

This study was based on reports from the following centers within the European Cooperative Group for Bone Marrow Transplantation (EBMT): Huddinge Hospital, Huddinge, Sweden (G. Gahrton, O. Ringdén, B. Lönnqvist, and P. Ljungman), University Hospital, Bologna, Italy (S. Tura), Hospital Jean-Minjoz, Besancon, France (M. Flesch), Cromwell Hospital, London, UK (P.J. Gravett and D. Guéret-Wardle), Pesaro Hospital, Pesaro, Italy (G. Lucarelli), University Hospital, Grenoble, France (M. Michallet, B. Corront, and D. Hollard) University Hospital, Pessac, France (J. Reiffers, G. Marit, and B. David) Hospital S Martin, Genova, Italy (M.T. van Lint), and University Hospital, Creteil, France (J.P. Vernant).

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