ALLOGENEIC BONE MARROW TRANSPLANTATION IN MULTIPLE MYELOMA

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Abstract *Background and Methods.* In contrast to autologous bone marrow transplants for hematologic cancers, allogeneic transplants contain no tumor cells that might cause a relapse. We report the results of such allogeneic bone marrow transplantation using HLA-compatible sibling donors in 90 patients with multiple myeloma performed in 26 European centers between 1983 and 1989.

Results. At the time of the most recent follow-up, 79 months after the start of the study, 47 patients were alive and 43 were dead. The rate of complete remission after bone marrow transplantation was 43 percent for all patients and 58 percent for the patients who had engraftment. The actuarial survival at 76 months was 40 percent. The median duration of relapse-free survival among patients who were in complete remission after bone marrow transplantation was 48 months.

The stage of the disease at diagnosis and the number of treatment regimens tried before bone marrow transplantation were predictive of the likelihood of complete remission after engraftment. There were trends toward longer survival among patients who were responsive to treatment before bone marrow transplantation, patients with Stage I disease at diagnosis, and patients who had received only first-line treatment before transplantation, as compared with those who were not responsive, those with Stage II or III disease at diagnosis, and those who had received three or more lines of treatment, but the differences in these factors were not statistically significant. Two post-transplantation factors predicted better long-term survival: complete remission after engraftment and grade I graft-versus-host disease, rather than grade II, III, or IV.

Conclusions. Allogeneic bone marrow transplantation with the use of HLA-matched sibling donors appears to be a promising method of treatment for some patients with multiple myeloma. (N Engl J Med 1991;325:1267-73.)

MULTIPLE myeloma is a fatal disorder with a median survival of about 36 months after conventional chemotherapy.[1-3] Even so, more than 50 percent of patients with multiple myeloma respond to first-line therapy, and some patients may even have a complete remission, defined as no detectable monoclonal immunoglobulin in the serum, no light chains in the urine, and no apparent myeloma cells in the bone marrow. Complete remission may occur after conventional intermittent therapy with melphalan plus prednisolone or with multidrug combination chemotherapy. More intensive chemotherapy seems to increase the fraction of patients entering complete remission, particularly if the treatment ablates the bone marrow, and is therefore combined with the rescue of autologous marrow.[4-7] The lesson from the use of such

treatment in patients with leukemia is that the fraction of patients with sustained complete remission can be increased.[8-11] Some patients may be permanently cured of their disease.

In comparison with autologous bone marrow transplantation, allogeneic transplantation has the advantage that the graft has no tumor cells that may subsequently cause a relapse. Also, a possible graft-versus-tumor effect may be induced by allogeneic bone marrow transplantation[12,13] but not by autologous transplantation. Members of the European Group for Bone Marrow Transplantation have therefore attempted to give patients with multiple myeloma intensive cytotoxic drug therapy with or without total-body irradiation before allogeneic bone marrow transplantation is performed.[14-16] This is a report of such an approach to bone marrow transplantation with the use of HLA-identical sibling donors. These procedures were performed at centers in Europe and reported to the registry of the European Group for Bone Marrow Transplantation at Huddinge Hospital from the establishment of the registry in 1983 until the end of 1989.

METHODS

Patients

Ninety patients with multiple myeloma who received a bone marrow graft from an HLA-compatible sibling donor from 1983 to the end of 1989 were reported to the European Group for Bone Marrow Transplantation registry. Fifty were men, and 40 were women. The median age was 42 years (range, 23 to 55). In 44 patients the malignant cells produced IgG; in 25, IgA; in 2, IgD; and in 15, light chains; 1 had a nonproducing multiple myeloma; and 3 had plasma-cell leukemia. At diagnosis, 13 patients had Stage IA disease,

1 Stage IB, 14 Stage IIA, 1 Stage IIB, 52 Stage IIIA, and 9 Stage IIIB. At the start of the conditioning treatment, 16 had Stage IA disease, 22 IIA, 49 IIIA, and 3 IIIB.[17] Before allogeneic bone marrow transplantation, major lytic lesions were seen on x-ray films in 45 patients and minor ones in 26 patients; 19 patients had a normal bone structure. The median time from diagnosis to bone marrow transplantation was 19 months (range, 3 to 85).

Response to Treatment before Bone Marrow Transplantation

The treatment before bone marrow transplantation varied according to the guidelines at each center. Thirty-two patients received conventional intermittent therapy with melphalan plus prednisolone as first-line treatment, and 58 patients received 1 of 32 different drug combinations, most of which contained melphalan or cyclophosphamide in addition to other drugs. Twenty-five combinations of drugs were used for second-line treatment, and 14 combinations were used for subsequent approaches. After first-line treatment, 16 patients entered complete remission (defined as the absence of detectable monoclonal M component in the serum or detectable abnormal light chains in urine on conventional immunoelectrophoresis or immunofixation and the absence of apparent myeloma cells in the marrow on conventional cytologic analysis); 41 had partial remission (defined as a decrease in the serum M-component concentration that was more than 50 percent of the pretreatment value, a decrease in urinary light-chain excretion to less than 0.2 g per 24 hours, or both, combined with a hemoglobin level of more than 90 g per liter, a serum albumin level of more than 30 g per liter, and a serum calcium level of less than 2.61 mmol per liter); 18 had stable disease that did not respond to treatment; and in 13 the disease progressed (data were lacking on 2 patients). Fifty-seven of these patients were later given second-line treatment, and of these, 26 received third-line treatment because of poor response or progressive disease. Thus, at the time of conditioning for bone marrow transplantation, 7 patients were in complete remission, 34 were in partial remission, and in 49 the disease was unresponsive or progressing. Thirty-three of the patients were still receiving first-line treatment, 31 were receiving second-line treatment, and 26 were receiving third-line or more advanced lines of treatment at conditioning.

Conditioning Treatment for Bone Marrow Transplantation

The conditioning regimen before bone marrow transplantation was total-body irradiation plus cyclophosphamide in 33 patients; total-body irradiation plus cyclophosphamide and other drugs in 43 patients; total-body irradiation plus melphalan in 5 patients; cyclophosphamide plus busulfan in 6 patients; cyclophosphamide plus melphalan in 2 patients; and cyclophosphamide plus several other drugs in 1 patient.

Prevention of Graft-versus-Host Disease

Treatment for the prevention of graft-versus-host disease (GVHD) consisted of the administration of methotrexate plus cyclosporine in 34 patients, methotrexate alone in 3 patients, methotrexate plus prednisolone in 2 patients, and methotrexate plus cyclosporine and prednisolone in 7 patients. Cyclosporine alone was given to 10 patients, whereas 3 patients received cyclosporine plus prednisolone. Thirty-one patients received marrow that had been pretreated in order to prevent GVHD. The marrow was pretreated with monoclonal antibodies against T cells, either without further GVHD prophylactic measures (7 patients) or followed by additional methotrexate (3 patients), cyclosporine (8 patients), or cyclosporine plus prednisolone (2 patients). T cells were removed in 11 patients before GVHD prophylaxis with cyclosporine (10 patients) or cyclosporine plus prednisolone (1 patient).

Statistical Analysis

Standard statistical methods were used. A comparison of frequencies of complete remission between groups was made with Fisher's exact test, and trends toward higher frequencies of complete remission with more lines of treatment were calculated by the chi-square test. Survival analyses were performed by the Kaplan–Meier method, and the prognostic groups were compared by the log-rank test.

RESULTS

Response to Bone Marrow Transplantation

The remission status of 67 of the 90 patients could be evaluated after bone marrow transplantation (Tables 1, 2, and 3). Eighteen patients died before engraftment and therefore could not be evaluated, and five patients could not yet be evaluated concerning engraftment. Of the 67 patients who could be evaluated, 39 were in complete remission after bone marrow transplantation. Six of these patients were in complete remission before conditioning, and the other 33 patients entered complete remission later. Twenty-eight patients had signs of multiple myeloma after engraftment.

The response to bone marrow transplantation was highly dependent on the status before conditioning. Of the 33 patients who underwent bone marrow transplantation while receiving first-line treatment, 20 were in complete remission after engraftment, whereas only 11 of 31 patients who underwent transplantation while receiving second-line treatment and 8 of 26 patients who underwent transplantation while receiving third-line or more advanced lines of treatment entered complete remission. The trend toward a higher rate of remission with fewer lines of treatment was significant ($P = 0.01$) (Table 1). The status immediately before conditioning did not significantly predict the response to bone marrow transplantation, except in those who were in complete remission before transplantation (Table 2). However, only 8 of 27 patients with progressive disease entered complete remission, and 21 of 41 who were in complete or partial remission before transplantation were in complete remission after transplantation.

The stage of the disease at diagnosis as well as before conditioning was an important predictor of remission status after bone marrow transplantation (Table

Table 1. Rates of Complete Remission after Bone Marrow Transplantation (BMT), According to the Number of Treatment Lines before Transplantation.

No. of Treatment Lines before BMT	No. of Patients		Complete Remission after BMT		
	Total	Evalu- ated*	No. of Patients	% of Total	% of Those Evaluated†
1	33	25	20	61	80
2	31	24	11	35	46
≥3	26	18	8	31	44
Total	90	67	39	43	58

*The number of patients who could be evaluated after bone marrow transplantation.

†There was a significant ($P = 0.01$) trend toward a higher frequency of remission with fewer lines of treatment (by the chi-square test). The fraction of patients in complete remission after bone marrow transplantation was significantly ($P = 0.006$) higher among patients who received only one line of treatment before bone marrow transplantation than among those who received two or more lines of treatment (by Fisher's exact test).

Table 2. Rates of Complete Remission after Bone Marrow Transplantation (BMT), According to Status Immediately before Conditioning.

STATUS BEFORE CONDITIONING	NO. OF PATIENTS		COMPLETE REMISSION AFTER BMT		
	TOTAL	EVALUATED*	NO. OF PATIENTS	% OF TOTAL	% OF THOSE EVALUATED
Complete remission	7	6	6	67†	100†
Partial remission	34	26	15	44	58
No response	22	18	10	45	56
Disease progression	27	17	8	30	47
Total	90	67	39	43	58

*The number of patients who could be evaluated after bone marrow transplantation.

†P = 0.039 for the comparison with the values for all other groups (by Fisher's exact test).

3). After bone marrow transplantation, 11 of 14 patients with Stage I disease at diagnosis were in complete remission, as were 5 of 15 with Stage II disease at diagnosis and 23 of 61 with Stage III disease at diagnosis. The corresponding figures for the stage of disease before conditioning were 10 of 16, 10 of 22, and 19 of 52.

Bone Lesions

Roentgenographic changes in bone lesions could be evaluated in 58 of the 90 patients. Patients who died before day 100 or who had not yet reached that point were considered unsuitable for evaluation. Bone lesions were largely unaffected by bone marrow transplantation. In only seven patients did the severity of the lesions decrease: major lytic lesions changed to minor lesions in three patients, and minor lesions disappeared in four patients. In three patients, new bone lesions appeared, and in two there was progression of the disease.

GVHD

Eighty patients could be evaluated for the presence of acute GVHD. It was absent in 37 patients; 22 had grade I GVHD, 13 had grade II, 4 had grade III, and 4 had grade IV. Ten patients could not be evaluated for acute GVHD because they died too soon after bone marrow transplantation. There was no apparent difference in the severity or frequency of GVHD between patients who were treated with methotrexate, cyclosporine, or a combination of these drugs and patients who had been given bone marrow pretreated with monoclonal antibodies for T-cell depletion.

Survival and Disease-free Survival

The overall duration of survival after bone marrow transplantation is shown in Figure 1. The median length of survival was 26 months, and there was an actuarial rate of long-term survival of 40 percent at 76 months. Twelve patients were alive between 36 and 78 months after bone marrow transplantation. There was no pretreatment factor that significantly predicted survival. Thus, the duration of survival was similar between patients above 40 years of age and those who

were 40 or younger and between men and women. There was a trend toward improved survival among patients who had Stage I disease at diagnosis as compared with patients with Stage II or III disease, but this was not statistically significant (Fig. 2). There was also a slight trend toward better long-term survival among patients who were in complete remission before conditioning, but this was also not statistically significant (Fig. 3). Patients who received only first-line treatment had a tendency toward better survival rates than the other groups of patients (Fig. 4). The rate of long-term survival was 47 percent among patients who underwent bone marrow transplantation within 12 months of diagnosis (n = 33), as compared with 28 percent among those who underwent transplantation more than 48 months after diagnosis (n = 13), but this difference was not significant (P = 0.07). No significant correlation was found when all patients were included in the analysis of the relation between survival and the time from diagnosis to bone marrow transplantation (P = 0.27). There was no difference in survival between patients who received conventional total-body irradiation plus cyclophosphamide and patients who received total-body irradiation and several other drugs or between these two groups and patients who received drug treatment alone (data not shown).

Postengraftment factors were more important in the prediction of outcome than preengraftment factors. Thus, survival was significantly better among patients who were in complete remission after engraftment than among those who had signs of multiple myeloma after engraftment (P = 0.0001) (Fig. 5). In addition, patients who had grade I GVHD did significantly better than patients with grade II, III, or IV GVHD (P = 0.004). Survival among patients who had no signs of GVHD was also better than that among patients with grade II, III, or IV GVHD (data not shown).

The median duration of relapse-free survival in 39

Table 3. Rates of Complete Remission after Bone Marrow Transplantation (BMT), According to the Stage of the Disease at Diagnosis.

STAGE AT DIAGNOSIS	NO. OF PATIENTS		COMPLETE REMISSION AFTER BMT		
	TOTAL	EVALUATED*	NO. OF PATIENTS	% OF TOTAL	% OF THOSE EVALUATED
IA	13	11	10	—	—
IB	1	1	1	—	—
Both	—	—	11	79†	91†
IIA	14	6	4	—	—
IIB	1	1	1	—	—
Both	—	—	5	33	71
IIIA	52	40	17	—	—
IIIB	9	8	6	—	—
Both	—	—	23	38	48
Total	90	67	39	43	58

*The number of patients who could be evaluated after bone marrow transplantation.

†P = 0.01 for the comparison of Stage I with Stage II and Stage III (by Fisher's exact test).

patients who were in complete remission after engraftment was 48 months. Eleven of these patients were still in complete remission 24 to 68 months after bone marrow transplantation.

Causes of Death

At the time of the most recent follow-up (an average of 79 months after the start of the study, 47 patients were alive and 43 patients had died. The causes of death were mainly the same as those in other patients with hematologic disorders who have undergone allogeneic bone marrow transplantation. The most common cause was interstitial pneumonia (nine patients), followed by recurrence of the original disease (eight), acute GVHD (six), bacterial and fungal infections (six), hemorrhage (five), organ failure (four), graft failure (two), adult respiratory distress syndrome (two), and the occurrence of a new cancer, namely leukemia (one).

DISCUSSION

A combination of chemotherapy and radiotherapy that ablates bone marrow and is followed by allogeneic bone marrow transplantation has previously been shown to produce long-term survival and a cure in some patients with acute leukemia and chronic myelocytic leukemia.[18-21] Preliminary attempts[14-16,22-24] have indicated that multiple myeloma may also be a disease that can be helped and perhaps cured by bone marrow transplantation. The present report shows that ablative total-body irradiation plus chemotherapy is effective in eradicating the multiple-myeloma cells. Although the group of patients that we studied was heterogeneous — most patients had advanced or late-stage disease — about 40 percent of all patients entered complete remission: about two thirds of the patients with Stage I disease and about one third of patients with Stage II or III disease. Complete remissions were induced in about half the patients who were responsive to treatment before transplantation and in about one third of those who were considered unresponsive to a previous treatment. More than half of those who received first-line treatment had a complete remission, whereas only about one fourth of those who had received three or more lines of treatment had a complete remission. Thus, pretreatment factors appear to be important in predicting the response to bone marrow transplantation. The relation to survival is less clear. There was a slight trend toward better survival among patients with Stage I disease at diagnosis or before conditioning, those who were in complete remission before transplantàtion, those who had received only first-line treatment, and those who underwent transplantation early in the course of the disease. However, these values were not significantly different from those for patients with Stage II or III disease, those in partial remission or unresponsive to treatment before conditioning, those who received more than one line of treatment, or
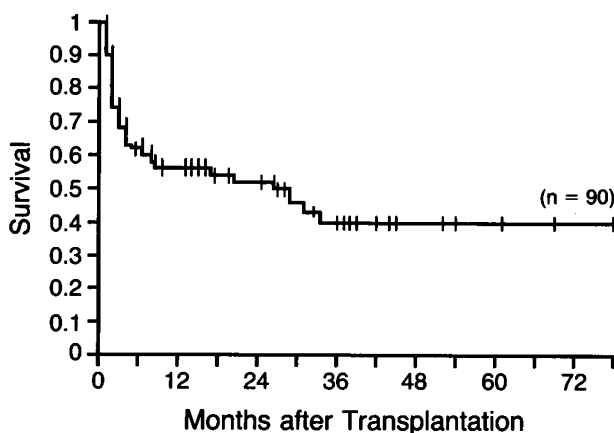

Figure 1. Kaplan–Meier Curve for Actuarial Survival after Bone Marrow Transplantation in All Patients.

those who underwent bone marrow transplantation later in the course of the disease. It is possible that future studies with larger numbers of patients will find that the survival of patients who have been treated with bone marrow transplantation early in the course of the disease is better than that of patients treated later, a finding that would be consistent with those in chronic myelocytic leukemia.[25] It is also possible that patients who respond to chemotherapy given immediately before bone marrow transplantation have a better prognosis after transplantation than those who do not respond to such chemotherapy. In our study, however, the projected rates of long-term survival in 49 patients with nonresponsive or progressive disease were 40 percent and 30 percent, respectively. Seven patients in these subgroups have survived between 36 and 78 months. Also, it is important to note that patients between 40 and 55 years of age should not be excluded from bone marrow
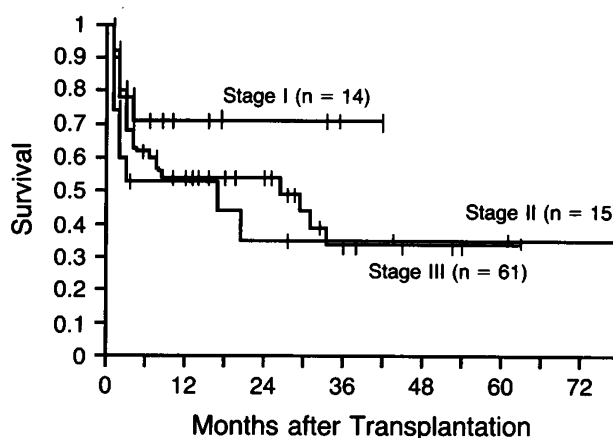

Figure 2. Actuarial Survival after Bone Marrow Transplantation, According to the Stage of the Disease at Diagnosis.
The Kaplan–Meier curves show a slight but not significant trend toward better survival among patients with Stage I disease at diagnosis than among patients with Stage II or III disease, but the difference was not significant.

transplantation. The predicted rate of long-term survival of this subgroup was 37 percent.

As could be expected, factors after transplantation were more predictive of survival than pretreatment factors. Thus, the rate of long-term survival was higher among patients who entered complete remission after engraftment than among those who did not. However, patients who did not have a complete remission after engraftment had a median survival of 21 months. Many such patients survive with minor signs of multiple myeloma for a relatively long time. This may be an indication of a graft-versus-tumor effect, which has previously been seen in patients with leukemia.[12,13,26] A temporary return to a premalignant stage is also a possibility. However, it appears that the persistence or reappearance of a monoclonal component eventually leads to relapse or progression of the disease.

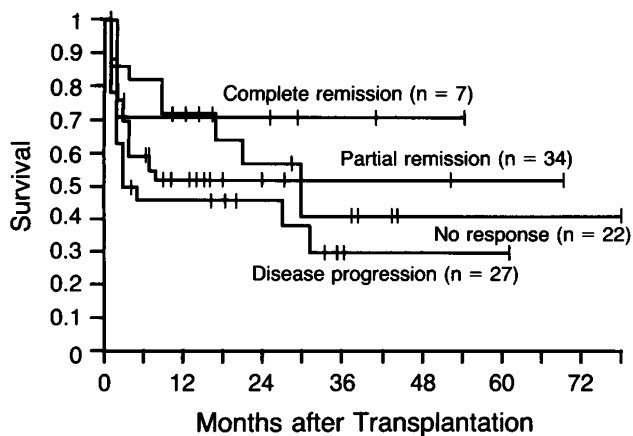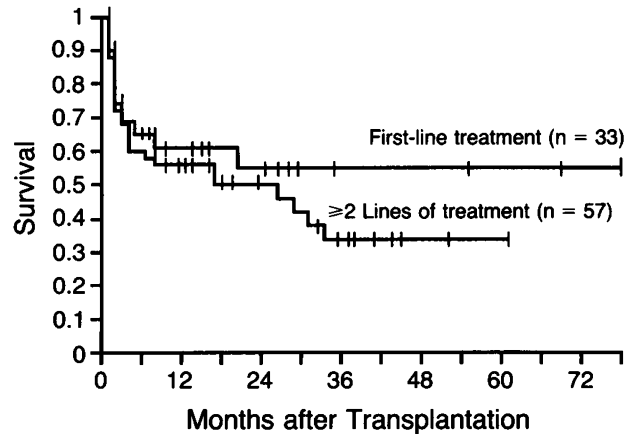GVHD did not seem to be a greater problem in

Figure 4. Actuarial Survival after Bone Marrow Transplantation, According to the Number of Lines of Treatment Regimens Used before Transplantation.

The Kaplan–Meier curves show a slight but not significant trend toward improved survival among patients who received only first-line treatment, as compared with those who received two or more lines of treatment.

Figure 3. Actuarial Survival after Bone Marrow Transplantation, According to Response Status before Conditioning.

The Kaplan–Meier curves show a tendency toward improved survival among patients with a better response before bone marrow transplantation, but the difference was not significant.

multiple myeloma than in other disorders. Only eight of the patients had grade III or IV GVHD. GVHD appeared to be another postengraftment predictive factor. Patients with grade III or IV GVHD had significantly poorer survival than those with grade I GVHD, irrespective of the method used to prevent GVHD. There was a slightly poorer survival rate among patients who did not have GVHD, as compared with those who had grade I GVHD. This would be consistent with a graft-versus-myeloma effect.

We can draw no conclusions as to whether allogeneic or autologous bone marrow transplantation is superior for the treatment of patients with multiple myeloma. Interesting attempts have been made with autologous bone marrow transplantation[27-31] or autologous peripheral-blood stem-cell grafting[32-35] after either high-dose melphalan or high-dose melphalan and

total-body irradiation, with or without other drugs. In such cases, there has been long-term survival of patients who were judged to have a poor prognosis with further conventional chemotherapy.[36]

In comparison with conventional chemotherapy, bone marrow transplantation seems superior for patients who have not responded to conventional treatment. The results of chemotherapy after an initial lack of response to treatment are disappointing.[37,38] The addition of interferon does not seem to change the results of chemotherapy in late-stage disease,[39] but it may be of importance when given in combination with chemotherapy in early stages of disease[40] or for the
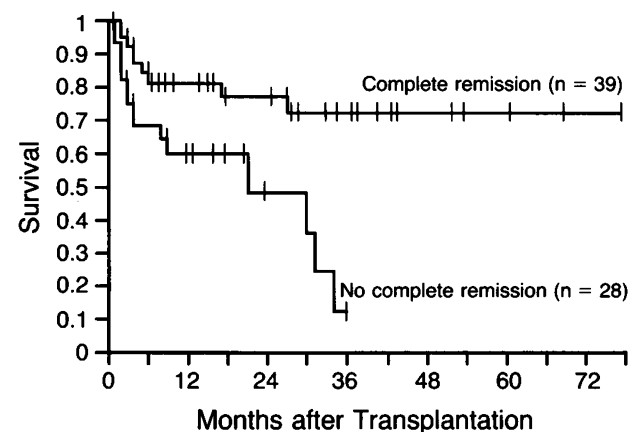
Figure 5. Actuarial Survival after Bone Marrow Transplantation, According to Whether Patients Were in Complete Remission after Engraftment.

The Kaplan–Meier curves show significantly (P = 0.0001 by two-sided log-rank test) better survival among patients who entered complete remission after engraftment than among those who did not.

treatment of patients with minimal persistent disease[41] — that is, those in partial or complete remission. Therefore, treatment with interferon after bone marrow transplantation may improve the overall results. Trials comparing posttreatment with interferon with no further treatment after bone marrow transplantation are warranted.

The optimal indication for bone marrow transplantation in multiple myeloma cannot be determined from the present study. However, some conclusions can be drawn. First, bone marrow transplantation in patients who are 40 to 55 years of age has a success rate similar to that in younger patients. Second, bone marrow transplantation seems to be a reasonable alternative for patients in whom first-line treatment has failed or who are unresponsive to such treatment. Third, transplantation may be offered earlier to patients who have factors that predict a poor prognosis with conventional chemotherapy, such as those with high levels of β_2-microglobulin or those with IgD or Stage III multiple myeloma.

APPENDIX

The following centers participated in the study by reporting patients to the myeloma registry at Huddinge Hospital: Clinical Hospital, Barcelona, Spain (A. Granena and J. Bladé); Transfusion Center, Besançon, France (M. Flesch); Hospital San Orsola, Bologna, Italy (S. Tura and M. Cavo); University Hospital, Pessac, France (J. Reiffers); Clinique Universitaire Saint-Luc, Brussels, Belgium (A. Ferrant); Centre Hospitalier et Universitaire de Caen, Caen, France (X. Troussard); Hôpital Henri Mondor, Créteil, France (J.P. Vernant); University Hospital, Essen, Germany (K. Quabeck); Hôpital Cantonal Universitaire de Genève, Geneva (B. Chapuis); Ospedale San Martino, Genoa, Italy (M.T. Van Lint); Hôpital des Sablons, Grenoble, France (M. Michallet); University of Helsinki, Helsinki, Finland (L. Volin); Huddinge University Hospital, Huddinge, Sweden (G. Gahrton, P. Ljungman, O. Ringdén, and B. Lönnqvist); University of Innsbruck, Innsbruck, Austria (D. Niederwieser); University Hospital, Leiden, the Netherlands (H. van Kamp); Hôpital Claude Huriez, Lille, France (T. Facon and J.P. Jouet); Charing Cross Hospital, London (D. Samson); London Clinic, London (P.J. Gravett); Royal Marsden Hospital, London, United Kingdom (P. Selby, M. Gore, and T.J. McElwain); University Hospital, Lund, Sweden (B. Sallerfors); Hôpital Saint Jacques, Nantes, France (J.-L. Harrouseau); University Hospital, Nijmegen, the Netherlands (T. de Witte); Group Hospitalier Cochin, Paris (B. Belanger); Pesaro Hospital, Pesaro, Italy (G. Lucarelli); Ospedale San Camillo, Rome (A. de Laurenzi); Dr. Daniel den Hoed Cancer Center, Rotterdam, the Netherlands (B. Löwenberg); Turku University, Turku, Finland (A. Toivanen, J. Nikoskelainen); University Hospital, Uppsala, Sweden (B. Simonsson); and University Hospital, Utrecht, the Netherlands (L. Verdonck).

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