Prognostic Factors in Allogeneic Bone Marrow Transplantation for Multiple Myeloma

By Gösta Gahrton, Sante Tura, Per Ljungman, Joan Bladé, Lena Brandt, Michele Cavo, Thierry Façon, Alois Gratwohl, Anton Hagenbeek, Peter Jacobs, Antonio de Laurenzi, M. Van Lint, Mauricette Michallet, Jukka Nikoskelainen, Josy Reiffers, Diana Samson, Leo Verdonck, Theo de Witte, and Liisa Volin

Purpose: **To analyze prognostic factors for allogeneic bone marrow transplantation (BMT) in multiple myeloma.**

Patients and Methods: **One hundred sixty-two reports of allogeneic matched sibling-donor transplants in multiple myeloma received by the European Group for Blood and Marrow Transplantation (EBMT) registry between 1983 and early 1993 were analyzed for prognostic factors. End points were complete remission, survival, and duration of complete remission.**

Results: **Following BMT, 44% of all patients and 60% of assessable patients entered complete remission. The overall actuarial survival rate was 32% at 4 years and 28% at 7 years. The overall relapse-free survival rate of 72 patients who were in complete remission after BMT was 34% at 6 years. Favorable pretransplant prognostic factors for survival were female sex (41% at 4 years), stage I disease at diagnosis (52% at 4 years), one line of previous treatment (42% at 4 years), and being in complete remission before conditioning (64% at 3 years). The subtype immunoglobulin A (IgA) myeloma and a low β_2-microglobulin level (< 4 g/L) also tended to have a favorable prognostic impact. The most important posttransplant prognostic factor was to enter a complete remission. Grade III to IV graft-versus-host disease (GVHD) was associated with poor survival.**

Conclusion: **Patients with a low tumor burden who respond to treatment before BMT and are transplanted after first-line therapy have the best prognosis following BMT.**

J Clin Oncol 13:1312-1322. © 1995 by American Society of Clinical Oncology.

MULTIPLE MYELOMA is a malignant disorder with a median survival duration of less than 3 years after conventional chemotherapy.[1-3] However, survival is highly variable. Some patients die within months, while occasional patients survive more than 10 years. This heterogeneity in the prognosis of multiple myeloma has encouraged studies of prognostic variables. A high tumor burden, high C-reactive protein level, high plasma-cell thymidine-labeling index, elevated β_2-microglobulin level, low serum albumin level, and low platelet count have been associated with extremely poor survival following conventional chemotherapy.[4-8] Therefore, such variables have been used to select patients for more intensive treatment. However, only a few studies have attempted to delineate prognostic factors of importance for the outcome of patients treated with high-dose chemotherapy followed by either autologous bone marrow transplantation (ABMT)[9,10] or allogeneic bone marrow transplantation (BMT).[11] In a previous study by the European Group for Blood and Marrow Transplantation (EBMT) of 90 patients with multiple myeloma who underwent BMT, a number of factors were found to influence long-term survival, including stage I disease at diagnosis, being in complete remission at transplantation, and having received only a few lines of treatment pretransplant.[11] The first patients reported to the EBMT registry in 1983 have now been monitored for up to 10 years. In the present updated report of 162 patients in the EBMT registry, new variables of prognostic importance have been found.

PATIENTS AND METHODS

Patients

One hundred sixty-two patients with multiple myeloma who received a bone marrow graft from an human leukocyte antigen (HLA)-compatible sibling donor between 1983 and early 1993 were reported to the EBMT registry; 92 were men and 70 were women. The median age was 43 years (range, 23 to 59). The myeloma subtype was immunoglobulin G (IgG) in 80 patients, IgA in 33, light chain in 31, and IgD in two. Five patients had nonsecretory multiple myeloma, and three had plasma-cell leukemia. The reports were incomplete in eight patients.

At diagnosis, 22 patients were in stage I, 30 in stage II (one IIB), and 109 in stage III (23 IIIB); stage was not reported in one patient. The median time from diagnosis to BMT was 14 months (range, 3 to 168).

Treatment Before BMT

Treatment before BMT varied according to center. Forty-one patients received conventional therapy with intermittent melphalan plus prednisolone as first-line treatment and 121 patients received other drug combinations, most of which contained melphalan or cyclo-

From the European Group for Blood and Marrow Transplantation; and Department of Medicine, Huddinge Hospital, Huddinge, Sweden.

Submitted October 6, 1994; accepted February 7, 1995.

Supported by European Commission, Bruxelles, Belgium, Concerted Action grant no. BMH1-CT94-0300; the Swedish Medical Research Council, Stockholm; and the Swedish Cancer Fund, Stockholm, Sweden.

Address reprint requests to Professor Gösta Gahrton, Department of Medicine, Huddinge Hospital, S-141 86 Huddinge, Sweden.

0732-183X/95/1306-0005$3.00/0

phosphamide in addition to other drugs. Thirty-six different combinations of drugs were used for second-line treatment and 21 combinations were used for subsequent treatment modalities. Twenty-six patients entered complete remission (defined as the absence of detectable monoclonal Igs in serum and of detectable free light chains in urine on either conventional immunoelectrophoresis or immunofixation, as well as the absence of apparent myeloma cells in the marrow on conventional cytologic analysis) after first-line treatment. Sixty-seven patients had a partial remission (defined as a decrease of serum Ig levels to a concentration less than 50% of pretreatment value, decrease in urine light-chain excretion to < 0.2 g/24 h, or both, combined with a hemoglobin value > 90 g/L, serum albumin level > 30 g/L, and serum calcium level < 2.61 mmol/L). Thirty-eight patients had stationary disease that did not respond to treatment, and in 20 patients the disease progressed (data were lacking for 11 patients). Ninety-six of these patients were later given second-line treatment, and of these, 46 patients received third-line treatment because of poor response or progressive disease. Thus, at the time of conditioning for BMT, 18 patients were in complete remission, 66 were in partial remission, 22 had stable disease that did not respond to further treatment, 14 had primary refractory disease, 25 had progressive disease despite treatment, and 14 were in relapse following complete or partial remission. Data were incomplete in three patients.

Conditioning Treatment for BMT

The conditioning for BMT was total-body irradiation (TBI) plus cyclophosphamide alone in 55 patients, TBI plus cyclophosphamide and melphalan in 27 patients, and TBI plus other drug combinations in 35 patients. Forty-five patients received high-dose chemotherapy without TBI. Twenty-five of these patients were conditioned with busulfan plus cyclophosphamide.

Prevention of Graft-Versus-Host Disease

Treatment for the prevention of graft-versus-host disease (GVHD) varied. Twenty-one different combinations of T-cell depletion, methotrexate, cyclosporine, prednisone, prednisolone, and cyclophosphamide were used. The single most common combination was cyclosporine plus methotrexate, which was used in 74 patients. Other drug combinations without T-cell depletion were used in 33 patients. T-cell depletion combined with drugs was used in 41 patients and alone in 13 patients. In one patient, information was lacking. Evaluation of GVHD was possible in 134 patients, of whom 46 received T-cell–depleted marrow, alone or in combination with drugs.

Statistical Analysis

Comparison of frequencies of complete remission was made with the conventional χ^2 test or, when small numbers made the χ^2 test improper, with Fisher's exact test. Survival curves were generated according to the Kaplan-Meier method and were tested with the log-rank test. Kaplan-Meier curves were dicotomized when less than five patients were under observation. Multivariate survival analyses were made with proportional hazards regression, with all quantitative variables dicotomized into qualitative variables.

RESULTS

Response to BMT

Remission status posttransplant was assessable in 121 patients. Forty-one patients either died before engraftment or were not yet assessable for engraftment. Of 121 patients who could be evaluated, 72 were in complete remission following BMT, of whom 16 were already in complete remission before conditioning for BMT. The median time from BMT to complete remission was 3 months, and in 90% of patients who entered complete remission, the monoclonal component had disappeared at 12 months posttransplant. However, in a small number of patients, the monoclonal Ig persisted for longer time periods, and in two patients it persisted for 36 months then disappeared.

Table 1. Complete Remission Following BMT by Number of Lines of Treatment Before BMT

No. of Treatment Lines Pre-BMT	Total No. of Patients	No. of Evaluated Patients	CR Following BMT		
			No. of Patients	% of Total	% of Evaluated
1	64	49	36	56	73
2	50	41	19	38	46
≥ 3	46	29	16	35	55
Unknown	2	2	1		
Total	162	121	72	44	60

Abbreviation: CR, complete remission.

The response to BMT was highly dependent on factors before conditioning. Forty-nine of 64 patients who were on first-line treatment at the time of BMT were assessable for complete remission, and 36 of these 49 patients entered a complete remission, while only 19 of 41 evaluated patients who underwent transplantation while receiving second-line treatment and 16 of 29 evaluated patients who underwent transplantation while receiving third-line or later treatment entered a complete remission (Table 1). The difference in complete remission rate between those who were on first-line treatment compared with those who were on second or later lines of treatment was highly significant ($P = .008$).

The status immediately before conditioning was not significantly predictive for response to BMT, except for patients who were in complete remission before transplantation (Table 2). For those who were not in complete remission immediately before conditioning, 24%, 36%, and 50%, respectively, of the patients who had progressive disease, primary refractory disease, or stable but non-responsive disease entered a complete remission following BMT.

Other factors that were important predictors of response included stage of disease at diagnosis and patient sex. Irrespective of whether patients were transplanted in later stages of disease, those who were diagnosed in stage I had a significantly higher response rate than those who

Table 2. Complete Remission by Status at Conditioning

Status at Conditioning Before BMT	Total No. of Patients	No. of Evaluated Patients	CR Following BMT		
			No. of Patients	% of Total	% of Evaluated
CR	18	16	15	83	94
Partial remission	66	52	28	42	54
Stable disease	22	20	11	50	55
Primary refractory	14	8	5	36	63
Progressive disease	25	14	6	24	43
Relapse	14	9	6	43	67
Unknown	3	2	1		
Total	162	121	72	44	60

were diagnosed in stage II or stage III ($P < .05$) (Table 3). IgG myeloma had a significantly poorer complete remission rate than other subtypes (Table 4). Male patients also had a poorer response than females.

Bone Lesions

Bone lesions could be evaluated in 98 patients by roentgenography. Patients who did not survive day 100 were not assessable. Twenty-two of 98 patients had a normal roentgenographic picture before transplantation; 17 did not change following transplantation, while five progressed. Twenty-three patients had minor lytic lesions or osteoporosis; six improved, 10 were stationary, and seven progressed. Fifty-three patients had major lytic lesions; six improved and 47 were stationary. Thus, in 57 of 76 patients who had bone changes before BMT, the roentgenographic bone pattern did not change following BMT.

GVHD

One hundred thirty-four patients could be evaluated for GVHD. It was absent in 50 (37%). Forty-three had grade I, 29 grade II, six grade III, and six grade IV. Because of the many various GVHD prevention methods used, it was difficult to analyze any specific preventive method separately. However, if T-cell depletion was included in the preventive method, alone or together with other treatment modalities, the fraction of patients who had grade II to IV GVHD was significantly less than if no T-cell depletion was used ($P = .02$) (Table 5).

Table 4. Complete Remission Following BMT by Subtype

Diagnosis	Total No. of Patients	No. of Evaluated Patients	CR Following BMT		
			No. of Patients	% of Total	% of Evaluated
IgG	80	58	27	34	47
IgA	33	25	17	52	68
Light chain	31	23	18	58	78
Other	18	15	10	56	67
Total	162	121	72	44	60

Survival and Disease-Free Survival

The overall median survival duration after BMT was 17 months (Fig 1). The 4-year survival rate was 32% and the 7-year survival rate 28%. One patient has survived for 10 years.

Univariate Analysis

Females had significantly better survival than males ($P = .04$) (Fig 2), but there was no significant difference in survival between patients less than 40 years of age and those $\geq$ 40 years (n = 55) ($P = .18$).

Patients with stage I disease at diagnosis had a significantly better survival than those diagnosed in stages II and III ($P = .05$) (Fig 3).

Patients with IgA myeloma tended to have better survival than patients with IgG myeloma ($P = .08$) and those with light-chain myeloma ($P = .28$) (Fig 4). There was no apparent difference between patients with λ- or κ-chain myeloma.

The level of β_2-microglobulin was measured in 45 patients at the time of diagnosis. There was a tendency for better survival in patients who had β_2-microglobulin values less than 4 mg/L as compared with those who had a higher value (Fig 5).

Patients who had received only one line of treatment had significantly better survival than those who had re-

Table 3. Complete Remission Following BMT by Stage at Diagnosis

Stage at Diagnosis	Total No. of Patients	No. of Evaluated Patients	CR Following BMT		
			No. of Patients	% of Total	% of Evaluated
I	22	19	15	68	79
II	30	18	11	37	61
III	109	83	45	41	54
Unknown	1	1	1		
Total	162	121	72	44	60

Table 5. T-Cell Depletion and GVHD

GVHD Prevention	Total No. of Evaluated Patients	Grade of GVHD (% of evaluated patients)				
		Absent	I	II	III	IV
T-cell depletion with or without other treatment	46	48	35	13	0	4
No T-cell depletion	88	32	31	26	7	5
Total evaluated	134	37	32	22	4	4

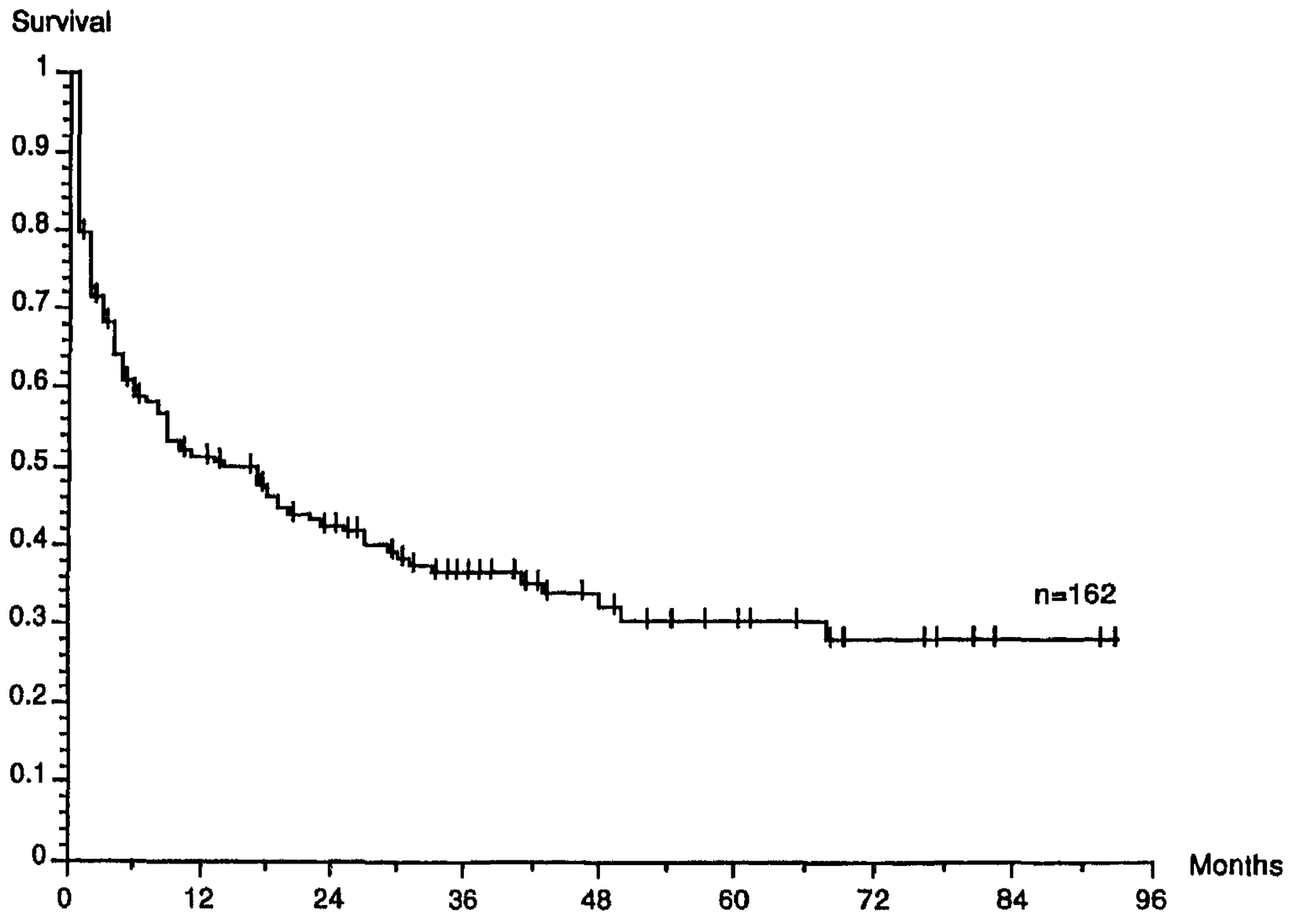

Fig 1. Actuarial survival in 162 patients who underwent allogeneic BMT.

ceived three or more lines of treatment ($P = .02$) (Fig 6). There was also a tendency for better survival in patients who had received only one line of treatment as compared with those who had received two lines of treatment ($P = .24$).

The status at conditioning was of importance. Patients who were in complete remission at the time of conditioning had significantly better survival than other patients ($P = .05$). However, within the groups partial remission, stable but nonresponsive disease, primary refractory dis-

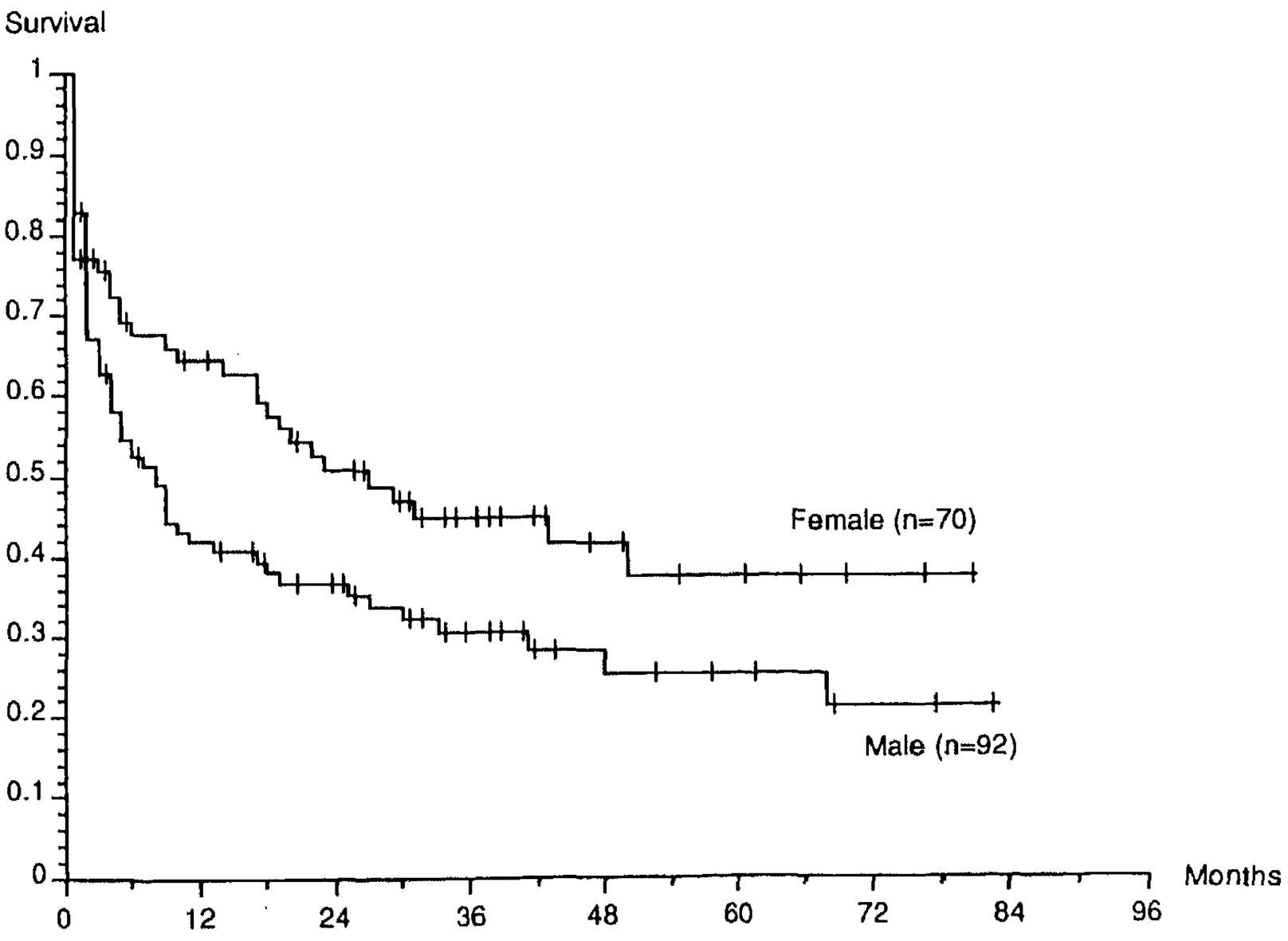

Fig 2. Actuarial survival after BMT according to patient sex. Kaplan-Meier curves show significantly better survival among females than among males ($P = .04$).

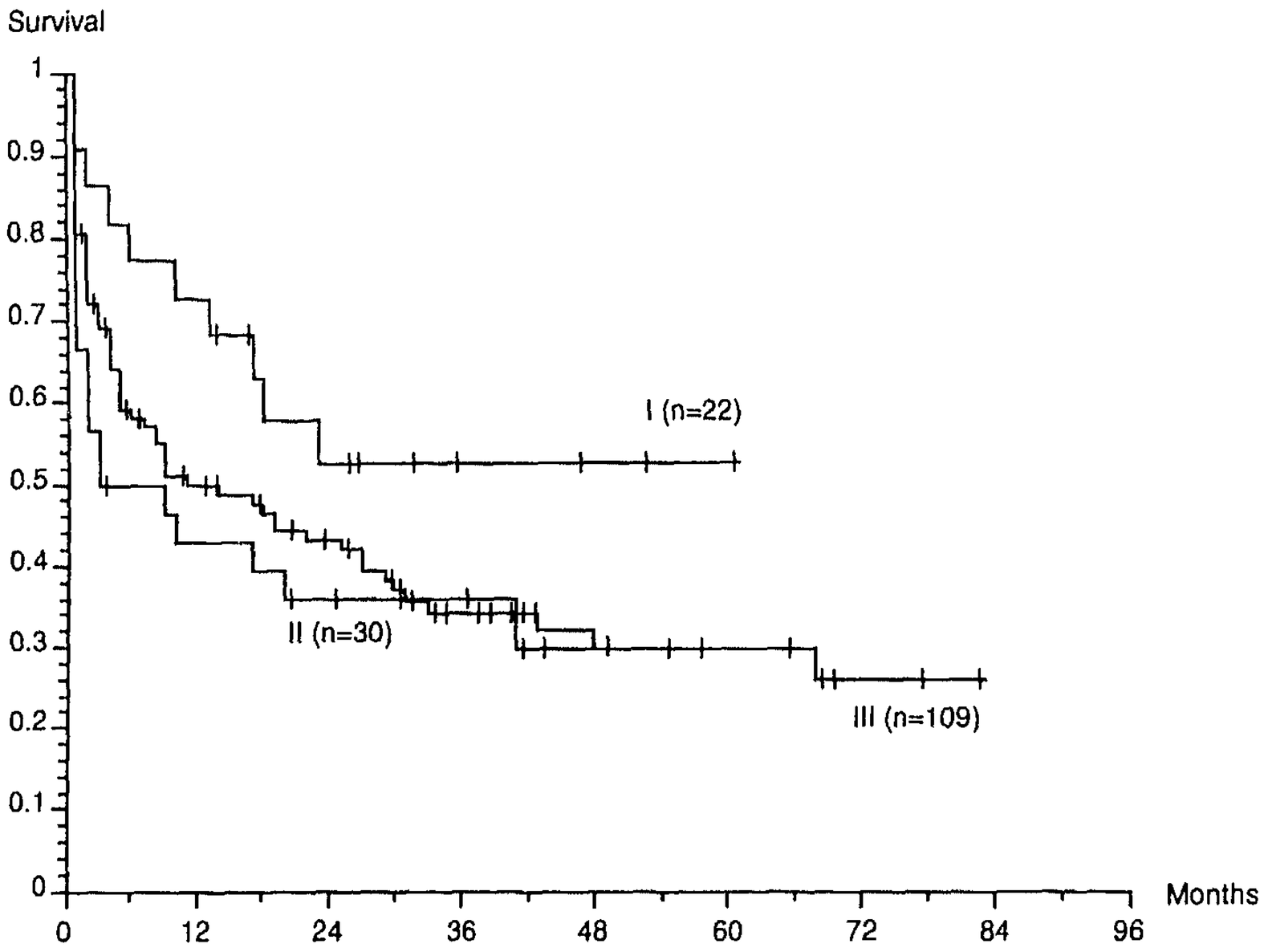

Fig 3. Actuarial survival after BMT according to stage of disease at diagnosis. Kaplan-Meier curves show significantly better survival among patients with stage I disease at diagnosis than among those with stages II and III ($P = .05$).

ease, and relapse or progressive disease, there was no significant difference.

The time from diagnosis to transplant was not of significant importance for survival. However, there was a tendency for patients who were transplanted later than 6 months from diagnosis to do worse than those who were transplanted before 6 months from diagnosis. This tendency for poorer survival was weak, but strongest for

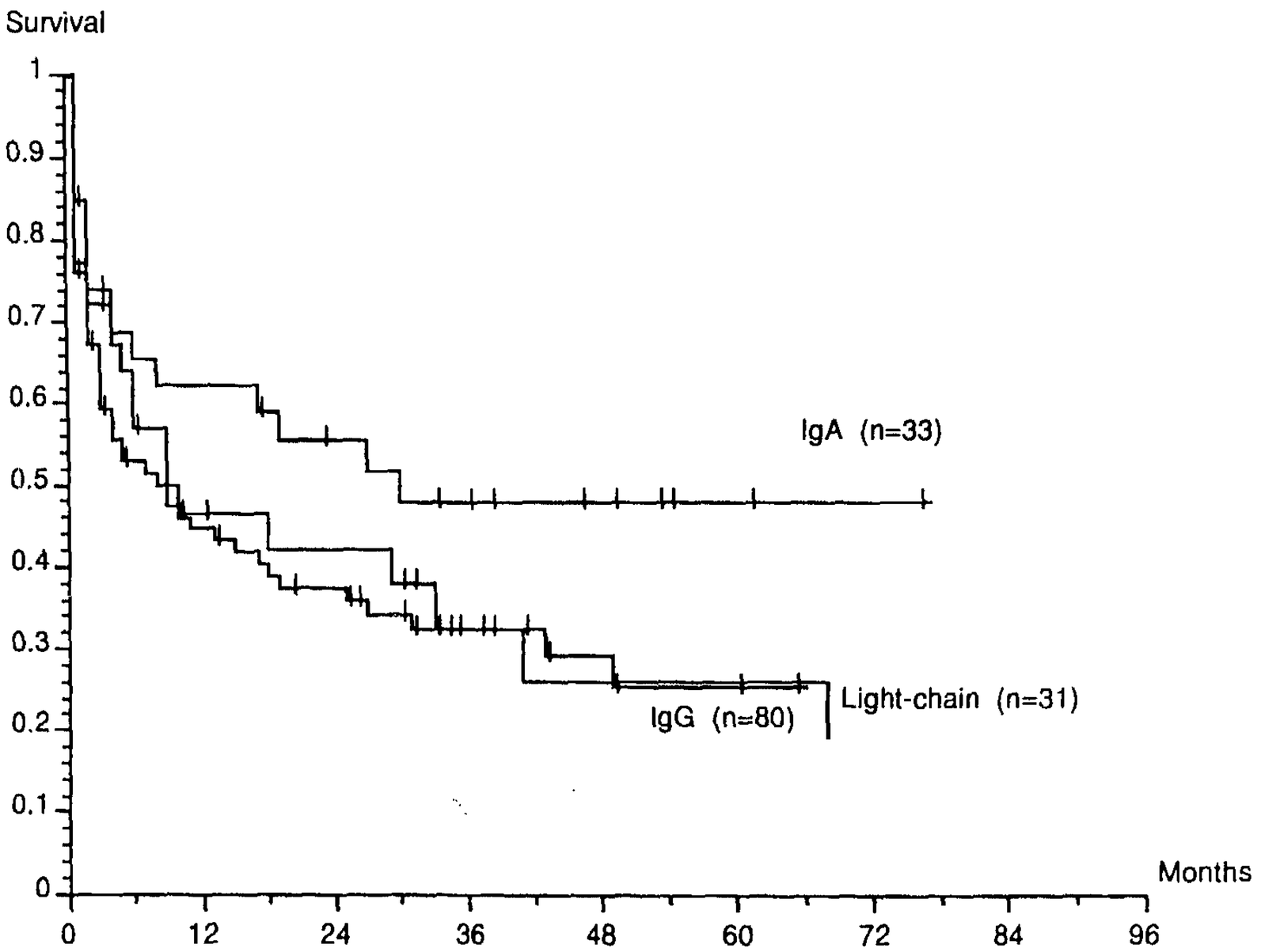

Fig 4. Actuarial survival after BMT according to myeloma subtype. Kaplan-Meier curves show a tendency for better survival among patients with IgA myeloma than among those with IgG ($P = .08$) or light-chain myeloma ($P = .28$).

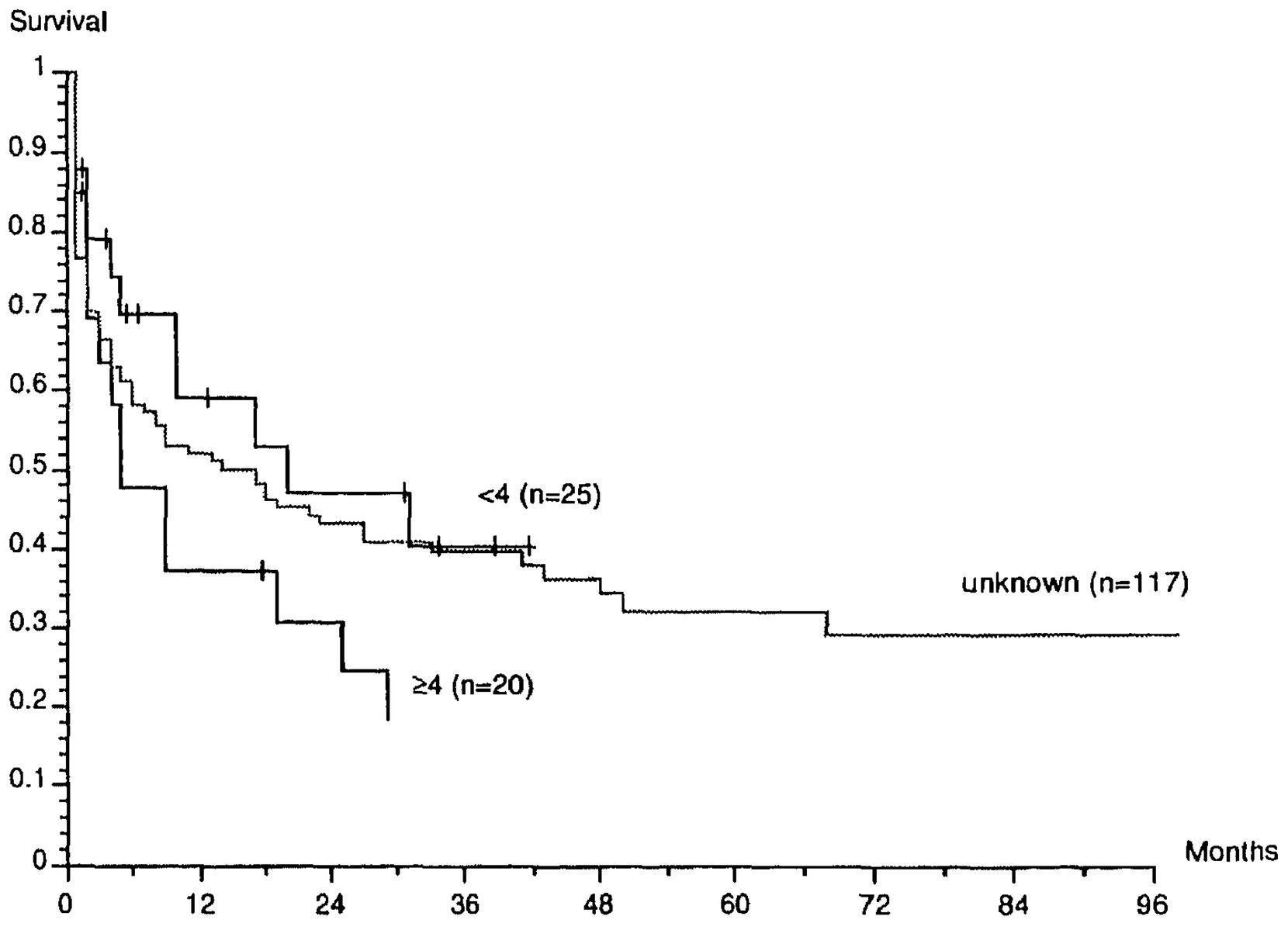

Fig 5. Actuarial survival after BMT according to β_2-microglobulin level at diagnosis. There was a slight, but nonsignificant trend, toward better survival among patients with values < 4 mg/L than among those who had values ≥ 4 mg/L.

patients who were transplanted later than 36 months from diagnosis ($P = .18$).

Bone marrow transplantation procedural factors of importance for prognosis could not be detected. However, the wide variety of regimens used made comparisons between different types of regimens difficult. The number of patients in each treatment group was small, so differences were unlikely to be detected. TBI plus cyclophos-

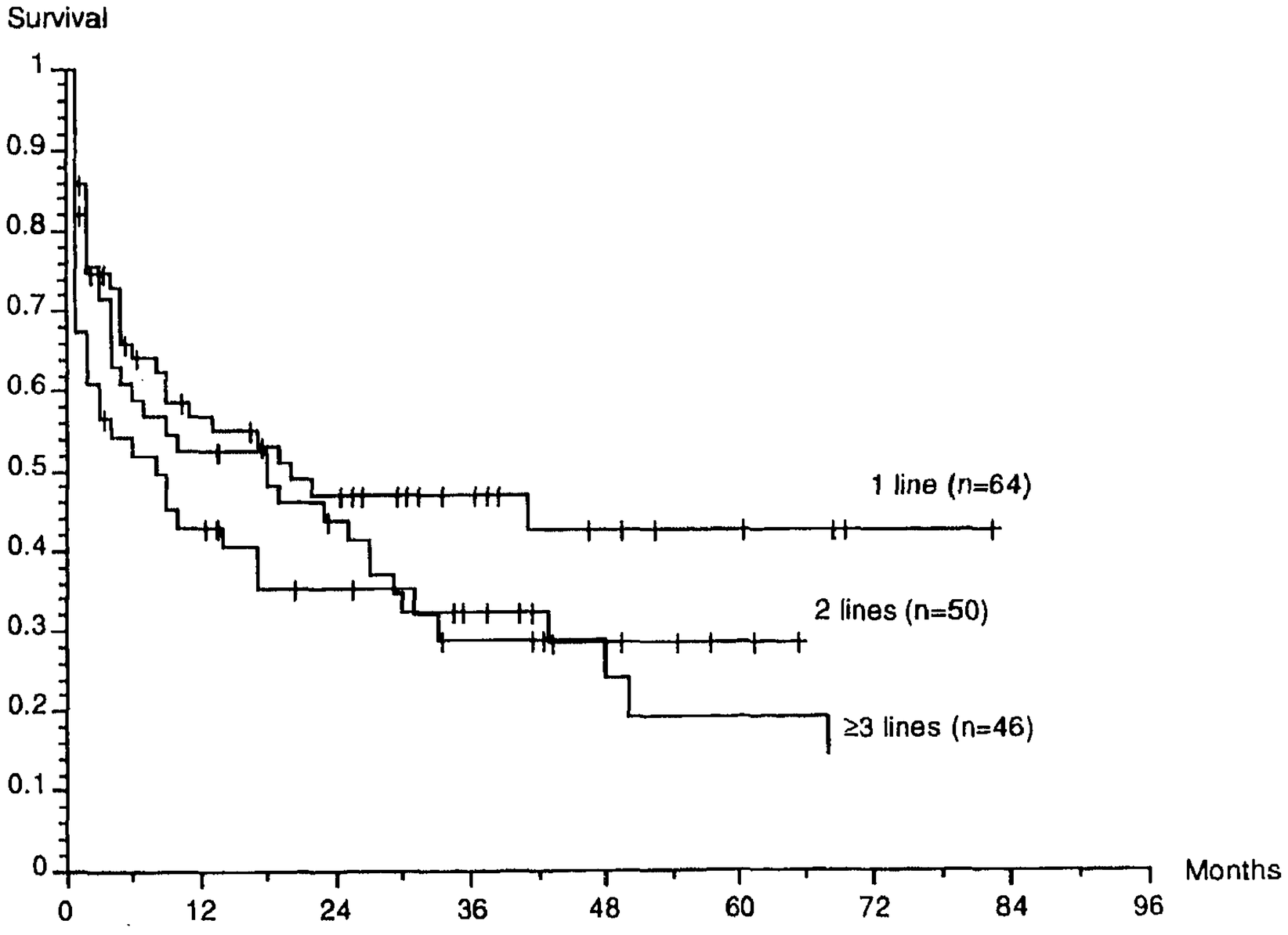

Fig 6. Actuarial survival after BMT according to number of lines of treatment regimens used pretransplantation. Kaplan-Meier curves show significantly better survival among patients who received only 1 line of treatment v those who received ≥ 3 lines of treatment ($P = .02$). There was also a tendency for better survival among patients who received only 1 line of treatment v those who received 2 lines of treatment (not significant).

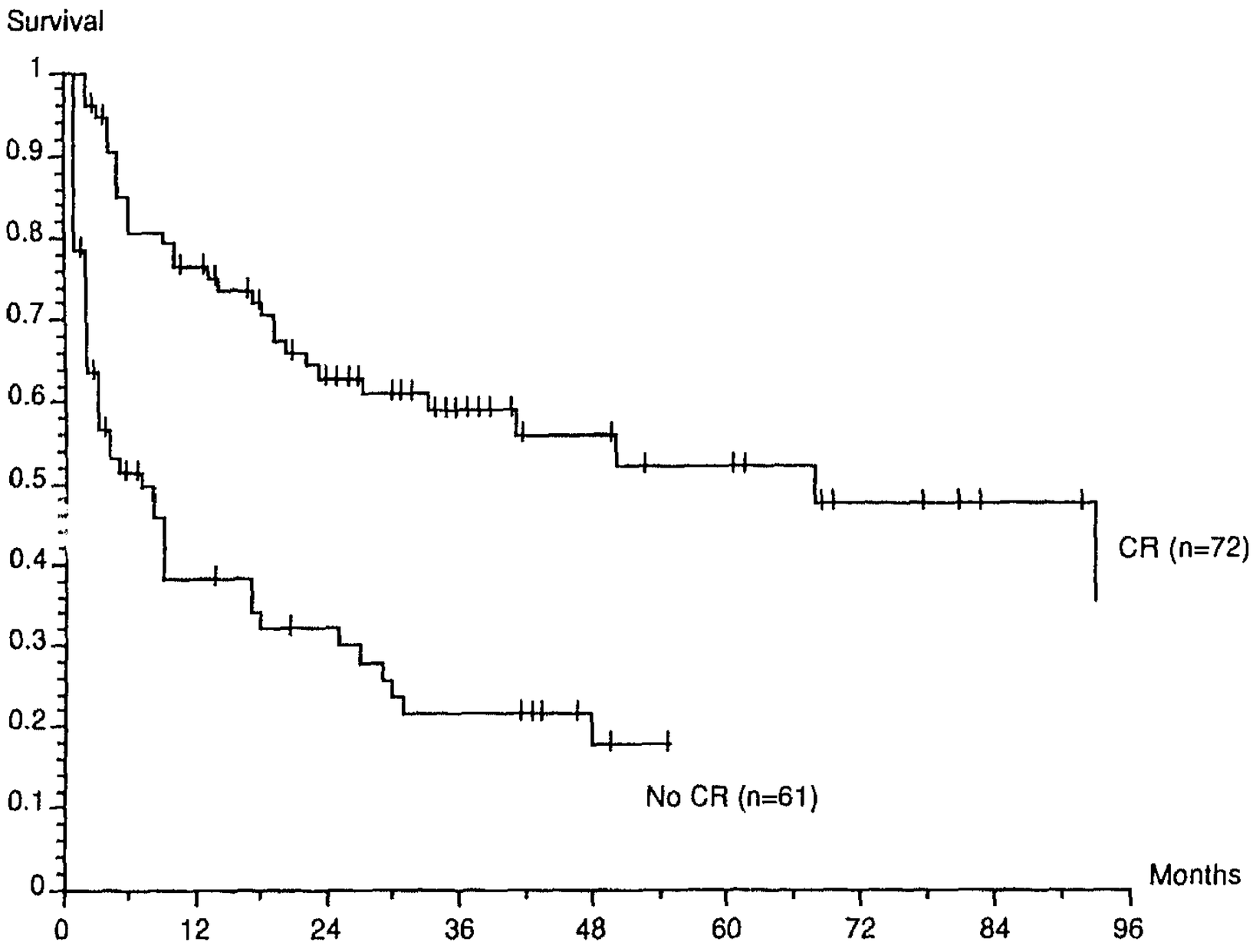

Fig 7. Actuarial survival after BMT according to whether patients were in complete remission (CR) after engraftment. Kaplan-Meier curves show significantly better survival among patients who entered CR after engraftment than among those who did not ($P = .001$).

phamide was the most commonly used conditioning method. There was no significant difference between this method and busulphan plus cyclophosphamide ($P = .24$). Although graft-versus-host prevention methods that included T-cell depletion resulted in fewer patients with GVHD grade II to IV and a greater fraction of patients without GVHD, this did not translate into a trend for better survival.

Postengraftment factors were also important predictors of survival. Patients who entered a complete remission following BMT had significantly longer survival than those who engrafted, but did not enter complete remission ($P = .001$) (Fig 7). The median survival duration for patients who were in complete remission following BMT was 60 months, and one patient in this group had survived for 10 years.

Patients who had GVHD grade III or IV had extremely poor survival. It was significantly poorer than for those who had grade I or II GVHD ($P = .02$). There was no significant difference between patients who had no GVHD and those who had grade I or II.

Multivariate Analysis

Multivariate analysis was attempted to estimate the significance and order of each risk factor. However, the material was probably too small for a fair analysis. No single pre-BMT factor came out as a significant risk factor, although there was a tendency for a higher risk for all of the factors that were significant in the univariate analysis. The strongest tendency for favorable survival in the multivariate analysis was female sex as opposed to male sex ($P = .07$) and being in stage I at diagnosis as opposed to being in other stages ($P = .11$). Of posttreatment prognostic factors, the most important adverse one was to have acute GVHD grade III or IV ($P = .0006$). Most important was the comparison between patients who entered a complete remission following BMT and those who did not. For fair comparison, only those patients who were not in complete remission before BMT, but entered complete remission following BMT, were compared with those who engrafted after BMT, but did not enter remission after BMT. Even then, patients who entered complete remission had significantly better survival ($P = .01$). The 5-year survival rate of patients who entered complete remission was 52% and the 7-year survival rate 47% (Fig 7).

Relapse Rate and Relapse-Free Survival

The relapse-free survival rate of patients who entered complete remission was 34% at 6 years (Fig 8). Nine patients are still in complete remission more than 4 years following transplantation. The overall relapse rate was 45% at 60 months (Fig 9). There was no significant difference between assessable patients who had received T-cell depletion or no T-cell depletion.

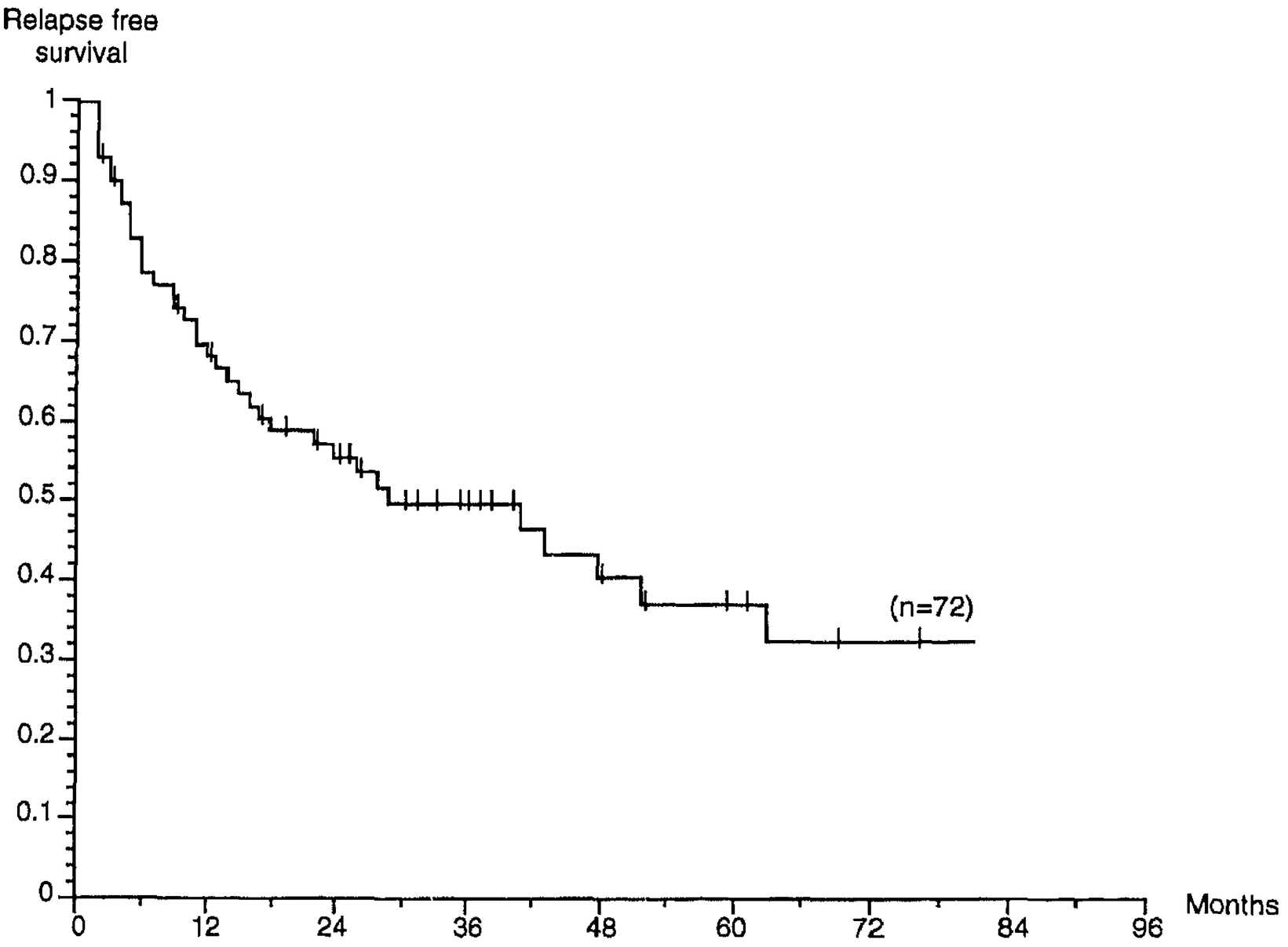

Fig 8. Actuarial relapse-free survival in 72 patients who entered complete remission following allogeneic BMT.

Causes of Death

At the time of analysis, 57 patients were alive and 103 had died. Two patients were lost for follow-up evaluation. The causes of death were mainly the same as those in other patients with hematologic disorders who have undergone BMT. The primary cause of death was the original disease in 27 patients, while in the others it was transplant-related, ie, bacterial or fungal infections in 19,

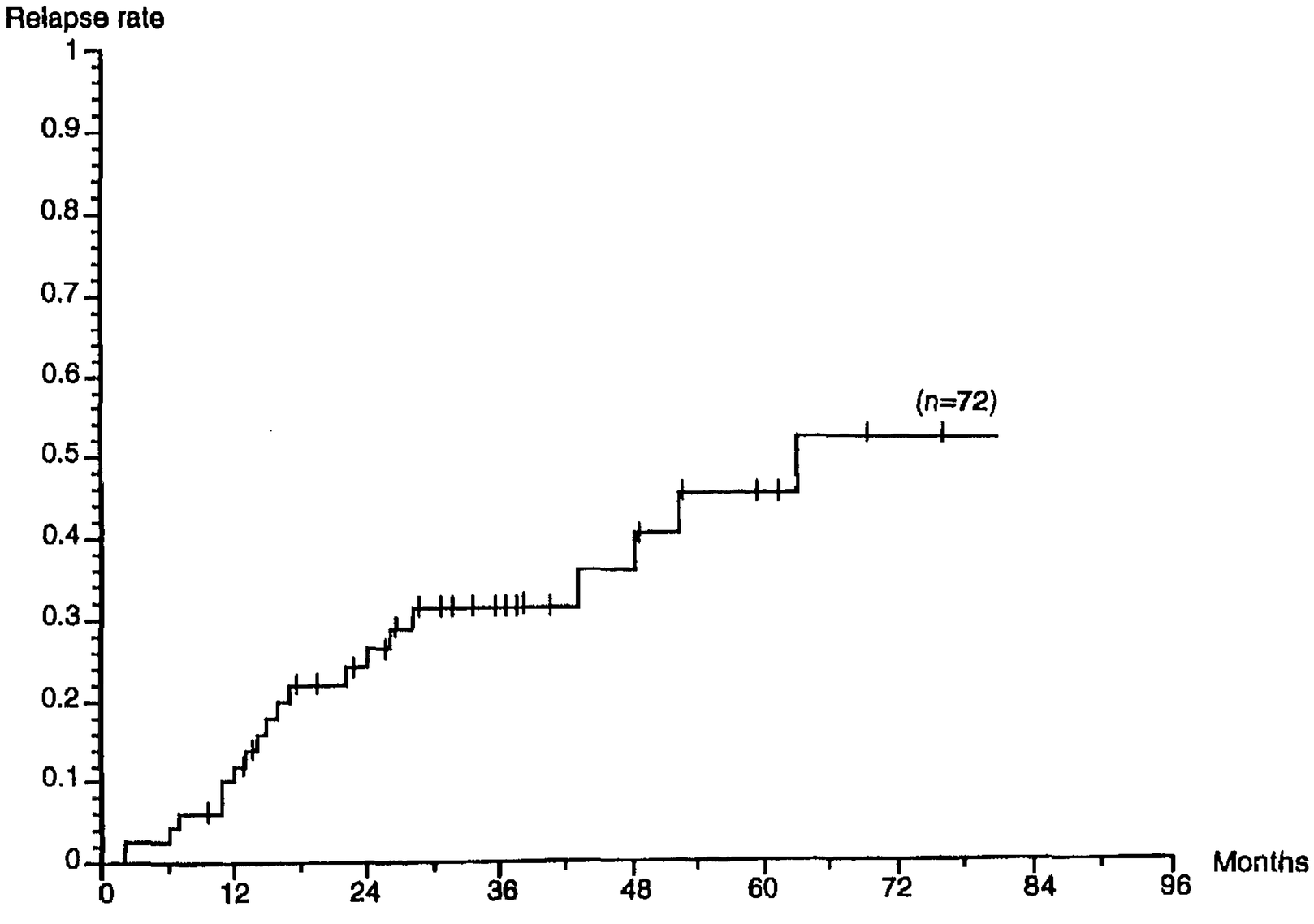

Fig 9. Relapse rate in 72 patients who underwent allogeneic BMT.

interstitial pneumonitis in 17, acute GVHD in 10, hemorrhage in seven, organ failure in six, adult respiratory distress syndrome (ARDS) in four, venooclusive disease in three, chronic GVHD in three, and other causes in seven.

DISCUSSION

We have previously reported that allogeneic BMT in multiple myeloma produces a high complete remission rate, with a fraction of patients entering sustained long-term complete remission.[11] Analysis of prognostic factors at that time demonstrated a significantly higher complete remission rate in patients with stage I disease at diagnosis, n patients who had received only one line of treatment, and in those who were in complete remission before conditioning for transplantation; however, although there were trends for longer survival in these patients, these were not statistically significant. In the present study, we were able to demonstrate significantly higher complete remission rates, and also significantly better survival in patients who were in stage I at diagnosis, who had received only one line of treatment before bone marrow transplantation, or who were in complete remission before conditioning as compared, respectively, with patients who were in later stages at diagnosis, had received two or more lines of treatment, or were not in complete remission before conditioning. In addition, we observed that females have a higher complete remission rate and better survival than males. In BMT for leukemia, the reason for a similar difference appears to be that results are poorer if female marrow is given to male recipients, than if female marrow is given to female recipients.[12,13] A slight trend in this direction was seen, but it was not significant.

The age of the patient within the age bracket 23 to 59 years was not of significant importance for outcome. There was only a slight trend for patients less than 40 years to have better survival than older patients. This would agree with a recent study of patients with leukemia, which showed that the prognostic impact of age is small between 30 and $\geq$ 50 years.[14]

The response rate was higher for both IgA and light-chain myeloma than for IgG myeloma. However, only IgA myeloma tended to have a better survival than IgG myeloma. Such a difference has generally not been noted with conventional chemotherapy, except in patients treated with combinations of interferon and melphalan.[15] In one such study, patients with IgA or Bence-Jones–only myeloma had a significantly better response rate and survival than patients with IgG myeloma.[14]

A limited number of patients were investigated for β_2-microglobulin level at diagnosis. Patients with a high β_2-microglobulin level (> 4 mg/L) tended to do worse than those with β_2-microglobulin levels below this value. This was similar to the importance of β_2-microglobulin in patients treated with conventional chemotherapy[4,7,8] or ABMT.[16]

The importance of procedural factors for outcome is difficult to investigate in this heterogenously treated material. No superiority of any conditioning regimen to the conventional regimen of TBI plus cyclophosphamide was detectable. The follow-up time of patients treated with busulphan plus cyclophosphamide was shorter than for patients treated with TBI plus cyclophosphamide or other chemotherapeutic agents. Thus, it is difficult to make a fair comparison; however, the shape of the survival curve suggests that busulphan plus cyclophosphamide is not superior to any other treatment modality used. If anything, the tendency was for poorer survival, but it was not significant. Busulphan plus cyclophosphamide has recently been compared with TBI plus cyclophosphamide in a prospective, randomized study of other hematologic disorders by the Nordic Bone Marrow Transplant Group (NBMT).[17] Although no significant difference in overall survival was found, patients with more advanced disease had a significantly poorer survival using busulphan plus cyclophosphamide than TBI plus cyclophosphamide, and it appeared that venoocclusive disease and hemorrhagic cystitis were more frequent in the busulphan-plus-cyclophosphamide group. The combination of busulphan plus cyclophosphamide for BMT in myeloma has been extensively evaluated by the Seattle group,[18] who found that, in 12 of 15 assessable myeloma patients (N = 20), a complete remission was obtained, with complete remission defined as disappearance of the Ig assayed by immunofixation. The probability of survival at 3 years was 36%. As in the EBMT study, most patients had a relatively advanced stage of disease. Although this study was a phase I study that escalated the dosages of busulphan, it should be noted that four of 20 patients developed venooclusive disease. This seems to support our view that venooclusive disease may well be more common following busulphan plus cyclophosphamide as compared with TBI plus cyclophosphamide. Of 103 patients with myeloma who died in the present EBMT study, only three had venooclusive disease determined as the primary cause of death.

Graft-versus-host prevention methods varied and it was therefore difficult to analyze any particular methodology. With T-cell depletion, acute GVHD was absent in 48% of patients. Without T-cell depletion, it was absent in only 32%. However, the lower frequency of GVHD with T-cell depletion did not translate into better survival or result in a higher relapse rate in comparison to those who were not T-cell–depleted. Thus, it was not possible to

show in this study, as has been previously shown for BMT in leukemias,[19,20] that patients with GVHD grade I or II had a lower relapse rate than patients with no GVHD. Nor was it possible to show that T-cell depletion resulted in a higher relapse rate, as has previously been shown for chronic myelocytic leukemia.[13,21,22] However, it is possible that the heterogeneity in the present study has prevented the detection of such a possible graft-versus-myeloma effect, which would have been abolished or diminished by T-cell depletion.

The most important predictor for long-term survival following BMT was complete remission after engraftment. The difference between survival of patients who entered remission and patients who engrafted with signs of multiple myeloma was highly significant. Also, a substantial fraction of complete remittors are still in complete remission up to 10 years following transplantation. Thus, obtaining a complete remission is crucial for long-term survival. Persistance of myeloma cells, Igs in serum, or light chain in urine will probably inevitably result in disease progression. However, a sizeable fraction of patients with very poor prognostic parameters before transplantation survived for more than 2 years, although they did not enter complete remission. Thus, it is possible that BMT may prolong life even in a fraction of patients who do not enter remission following transplantation.

This prognostic factor analysis does not give conclusive help in selecting patients for allogeneic BMT. Since the best results are obtained in females, in patients who are diagnosed in stage I irrespective of whether they are transplanted in another stage, in patients who have received only one line of treatment, and in those who were in complete remission already before transplantation, such patients appear to be reasonable candidates. However, as these groups of patients may also have relatively good prognosis with other treatment modalities, such as ABMT, with a lower initial transplantation mortality, it is difficult at this stage to recommend allogeneic BMT unreservedly for all of these patient groups. Still, it seems reasonable to conclude that allogeneic BMT could be performed at a stage when first-line treatment fails or if the patient is unresponsive to first-line treatment. In such cases, survival with chemotherapy is usually poor. Also, BMT can be performed not only in patients less than 40 years of age but also in older patients, probably up to 55 years of age. Although factors that predict poor prognosis with conventional chemotherapy, such as stage III multiple myeloma and a high β_2-microglobulin level, also predict for relatively poor prognosis with transplantation, some patients might be candidates for BMT, since long-term survival is sometimes obtained. Patients with IgA myeloma seem to be especially good candidates for BMT.

The choice of treatment modality in multiple myeloma is becoming increasingly complex. Chemotherapy, ABMT, and allogeneic BMT are now competing methods. Although our results indicate that allogeneic BMT should preferably be done early, perhaps during or after failure of first-line treatment, and before several lines of treatment, comparative studies must be performed to determine the value of each treatment method. Controlled, prospective trials are extremely difficult to perform. For that reason, matched-pair analysis studies, as has been done for comparison of BMT and chemotherapy in acute leukemia,[23] may be more realistic to delineate factors that might guide selection of one or the other method. Such analyses are in progress.

APPENDIX

The following centers participated in the study by reporting patients to the Myeloma Registry at Huddinge Hospital Hospital: Centre Hospitalier Regional et Universitaire, Angers, France (M. Boasson); Hospital Clinic, Barcelona, Spain (J. Bladé, C. Rozman); Kantonspital, Basel, Switzerland (A. Gratwohl); Hopital Jean Minjoz, Besançon, France (M. Flesch); Hospital San Orsola, Bologna, Italy (M. Cavo, S. Tura); Institut Jules Bordet, Brussels, Belgium (L. Debusscher); Cliniques Universitaires St. Luc, Brussels, Belgium (A. Ferrant); Hopital Caen, Caen, France (X. Troussard); Groote Shuur Hospital, Cape Town, South Africa (P. Jacobs); Hopital Henri Mondor, Creteil, France (J.-P. Vernant); Universität Düsseldorf, Düsseldorf, Germany (K. Quabeck); Ospedale di Careggi, Firenze, Italy (F. Rossi); Hopital Cantonal Universitaire, Geneva, Switzerland (B. Chapuis); Ospedale San Martino, Genova, Italy (M. Van Lint); Hopital A. Michallon, Grenoble, France (C. Chabannon, M. Michallet); Medical School of Hannover, Hannover, Germany (H. Link); University of Helsinki, Helsinki, Finland (L. Volin); Huddinge Hospital, Huddinge, Sweden (G. Gahrton, P. Ljungman); Christian-Albrechts-University, Kiel, Germany (N. Schmitz); University Hospital, Leiden, The Netherlands (van de Loo); Hopital Claude Hurez, Lille, France (T. Façon); University Medical Center, Ljubljana, Slovenia (J. Pretnar); Royal Marsden Hospital, London, United Kingdom (P. Selby); The London Clinic, London, United Kingdom (P. Gravett); Royal London Hospital, London, United Kingdom (A.C. Newland); Charing Cross Hospital, London, United Kingdom (D. Samson); University Hospital, Lund, Sweden (B. Sallerfors); Hotel Dieu, Nantes, France (J.L. Harousseau); University Hospital, Nijmegen, the Netherlands (T. de Witte, A. Schattenberg); Hopital Cochin, Paris, France (C. Belanger); Pesaro Hospital, Pesaro, Italy (G. Lucarelli); Hopital du Haut Leveque, Pessac, France (J. Reiffers); S. Camillo Hospital, Roma, Italy (A. De Laurenzi); Dr Daniel Den Hoed Cancer Center, Rotterdam, the Netherlands (A. Hagenbeek); University Central Hospital, Turku, Finland (J. Nikoskelainen, A. Toivanen); and University Hospital, Utrecht, the Netherlands (L. Verdonck).

REFERENCES

1. Alexanian R, Haut A, Khan A, et al: Treatment for multiple myeloma: Combination chemotherapy with different melphalan dose regimens. JAMA 208:1680-1685, 1969

2. Sporn JR, McIntyre OR: Chemotherapy of previously untreated multiple myeloma patients: An analysis of recent treatment results. Semin Oncol 13:318-325, 1986

3. Österborg A, Åhre A, Björkholm M, et al: Alternating combination chemotherapy (VMCP/VBAP) is not superior to melphalan/prednisone in the treatment of multiple myeloma patients stage III—A randomized study from MGCS. Eur J Haematol 43:54-62, 1989

4. Durie BGM, Stock-Novack D, Salmon SE, et al: Prognostic value of pretreatment serum β_2 microglobulin in myeloma: A Southwest Oncology Group study. Blood 75:823-830, 1990

5. Cavo M, Calieni P, Zuffa E, et al: Prognostic variables and clinical staging in multiple myeloma. Blood 74:1774-1780, 1989

6. Bladé J, Rozman C, Cervantes F, et al: A new prognostic system for multiple myeloma based on easily available parameters. Br J Haematol 72:507-511, 1989

7. Bataille R, Boccadoro M, Klein B, et al: C-reactive protein and β-2 microglobulin produce a simple and powerful myeloma staging system. Blood 80:733-737, 1993

8. Greipp PR, Lust JA, O'Fallon M, et al: Plasma cell labeling index and β_2-microglobulin predict survival independent of thymidine kinase and C-reactive protein in multiple myeloma. Blood 81:3382-3387, 1993

9. Björkstrand B, Goldstone AH, Ljungman P, et al: Prognostic factors in autologous stem cell transplantation for multiple myeloma: An EBMT Registry study. Leuk Lymphoma 15:265-272, 1994

10. Harousseau JL, Attal M, Divine M, et al: Autologous hemopoietic stem cell transplantation (ASCT) in multiple myeloma. A report of the French Registry. Nineteenth Annual Meeting of the EBMT, Garmisch-Partenkirchen, Germany, January 17-21, 1993, p 68 (abstr 2301)

11. Gahrton G, Tura S, Ljungman P, et al: Allogeneic bone marrow transplantation in multiple myeloma. N Engl J Med 325:1267-1273, 1991

12. Zwaan FE, Hermans J, Barrett AJ, et al: Bone marrow transplantation for acute nonlymphoblastic leukaemia: A survey of the European Group for Bone Marrow Transplantation (EGBMT). Br J Haematol 56:645-653, 1984

13. Gratwohl A, Hermans J, Niederwieser D, et al: Bone marrow transplantation for chronic myeloid leukemia: Long-term results. Bone Marrow Transplant 12:509-516, 1993

14. Ringdén O, Horowitz MM, Gale RP, et al: Outcome after allogeneic bone marrow transplant for leukemia in older adults. JAMA 270:57-60, 1993

15. Österborg A, Björkholm M, Björeman M, et al: Natural interferon-alpha in combination with melphalan/prednisone versus melphalan/prenisone in the treatment of multiple myeloma stages II and III: A randomized study from the Myeloma Group of Central Sweden. Blood 81:1428-1434, 1993

16. Attal M, Huguet F, Schlaifer D, et al: Intensive combined therapy for previously untreated aggressive myeloma. Blood 79:1130-1136, 1992

17. Ringdén O, Ruutu T, Remberger M, et al: A randomized trial comparing busulfan with total body irradiation as conditioning in allogeneic marrow transplant recipients with leukemia: A report from the Nordic Bone Marrow Transplant Group. Blood 83:2723-2730, 1994

18. Bensinger WI, Buckner CD, Clift RA, et al: Phase I study of busulfan and cyclophosphamide in preparation for allogeneic marrow transplant for patients with multiple myeloma. J Clin Oncol 10:1492-1497, 1992

19. Weiden PL, Sullivan KM, Flournoy N, et al: Antileukemic effect of chronic graft-versus-host disease: Contribution to improved survival after allogeneic marrow transplantation. N Engl J Med 304:1529-1533, 1981

20. Horowitz MM, Gale RP, Sondel PM, et al: Graft-versus-leukemia reactions after bone marrow transplantation. Blood 75:555-572, 1990

21. Apperley JF, Jones L, Hale G, et al: Bone marrow transplantation for patients with chronic myeloid leukaemia: T-cell depletion with Campath-1 reduced the incidence of graft-versus-host disease but may increase the risk of leukaemia relapse. Bone Marrow Transplant 1:53-66, 1986

22. Marks DI, Hughes TP, Szydlo R, et al: HLA-identical sibling donor bone marrow transplantation for chronic myeloid leukaemia in first chronic phase: Influence of GVHD prophylaxis on outcome. Br J Haematol 81:383-390, 1992

23. Horowitz MM, Messerer D, Hoelzer D, et al: Chemotherapy compared with bone marrow transplantation for adults with acute lymphoblastic leukemia in first remission. Ann Intern Med 115:13-18, 1991