

ORIGINAL ARTICLE

A Comparison of Allografting with Autografting for Newly Diagnosed Myeloma

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ABSTRACT

BACKGROUND

In this trial of the treatment of newly diagnosed multiple myeloma, we compared a protocol that entailed a hematopoietic stem-cell autograft followed by an allograft from an HLA-identical sibling with a protocol of tandem autografts.

METHODS

We enrolled 162 consecutive patients with newly diagnosed myeloma who were 65 years of age or younger and who had at least one sibling. All patients were initially treated with vincristine, doxorubicin, and dexamethasone, followed by melphalan and autologous stem-cell rescue. Patients with an HLA-identical sibling then received nonmyeloablative total-body irradiation and stem cells from the sibling. Patients without an HLA-identical sibling received two consecutive myeloablative doses of melphalan, each of which was followed by autologous stem-cell rescue. The primary end points were overall survival and event-free survival.

RESULTS

After a median follow-up of 45 months (range, 21 to 90), the median overall survival and event-free survival were longer in the 80 patients with HLA-identical siblings than in the 82 patients without HLA-identical siblings (80 months vs. 54 months, $P=0.01$; and 35 months vs. 29 months, $P=0.02$, respectively). Among patients who completed their assigned treatment protocols, treatment-related mortality did not differ significantly between the double-autologous-transplant group (46 patients) and the autograft–allograft group (58 patients, $P=0.09$), but disease-related mortality was significantly higher in the double-autologous-transplant group (43% vs. 7%, $P<0.001$). The cumulative incidence rates of grades II, III, and IV graft-versus-host disease (GVHD) combined and of grade IV GVHD in the autograft–allograft group were 43% and 4%, respectively. Overall, 21 of 58 patients (36%) were in complete remission after a median follow-up of 38 months (range, 10 to 72) after allografting. Of the 46 patients who received two autografts, 25 (54%) died.

CONCLUSIONS

Among patients with newly diagnosed myeloma, survival in recipients of a hematopoietic stem-cell autograft followed by a stem-cell allograft from an HLA-identical sibling is superior to that in recipients of tandem stem-cell autografts. (ClinicalTrials.gov number, NCT00415987.)

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N Engl J Med 2007;356:1110-20.

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HIGH-DOSE CHEMOTHERAPY WITH RESCUE of the bone marrow by an autologous hematopoietic-cell transplant is regarded as the standard of care for newly diagnosed myeloma in patients under 65 years of age.¹⁻⁴ However, few patients who undergo the procedure are free of the disease for more than 10 years.^{2,3} Recurrences are due primarily to the failure of the chemotherapy to eradicate all myeloma cells. Lower relapse rates and longer remissions have been reported in patients receiving allogeneic stem-cell transplants, presumably because of the graft-versus-myeloma effects of the graft.⁵ The high risk of transplant-related mortality (30 to 60%) among young, medically fit patients has, however, limited the use of allogeneic transplants.⁶⁻⁹ Combining a cytoreductive autograft with a nonmyeloablative allograft has lowered transplant-related mortality to approximately 15%.^{10,11} However, it remains to be determined whether overall survival is longer with nonmyeloablative conditioning for an allograft than with intensive conditioning for a second autograft.¹² Here we report a study in which the sole criterion for the assignment of treatment in patients with newly diagnosed myeloma was the presence or absence of an HLA-identical sibling.

METHODS

PATIENTS

From September 1998 through July 2004, we enrolled 245 consecutive patients 65 years of age or younger with stage II or III myeloma at five Italian centers. Of these 245 patients, 199 had siblings, and 162 of the patients who had siblings underwent HLA typing to determine whether they had potential HLA-identical donors (Fig. 1). Written informed consent was obtained on enrollment, and the study was approved by the institutional review boards of the five centers and conducted according to the procedures of the Declaration of Helsinki.

TREATMENT ASSIGNMENTS

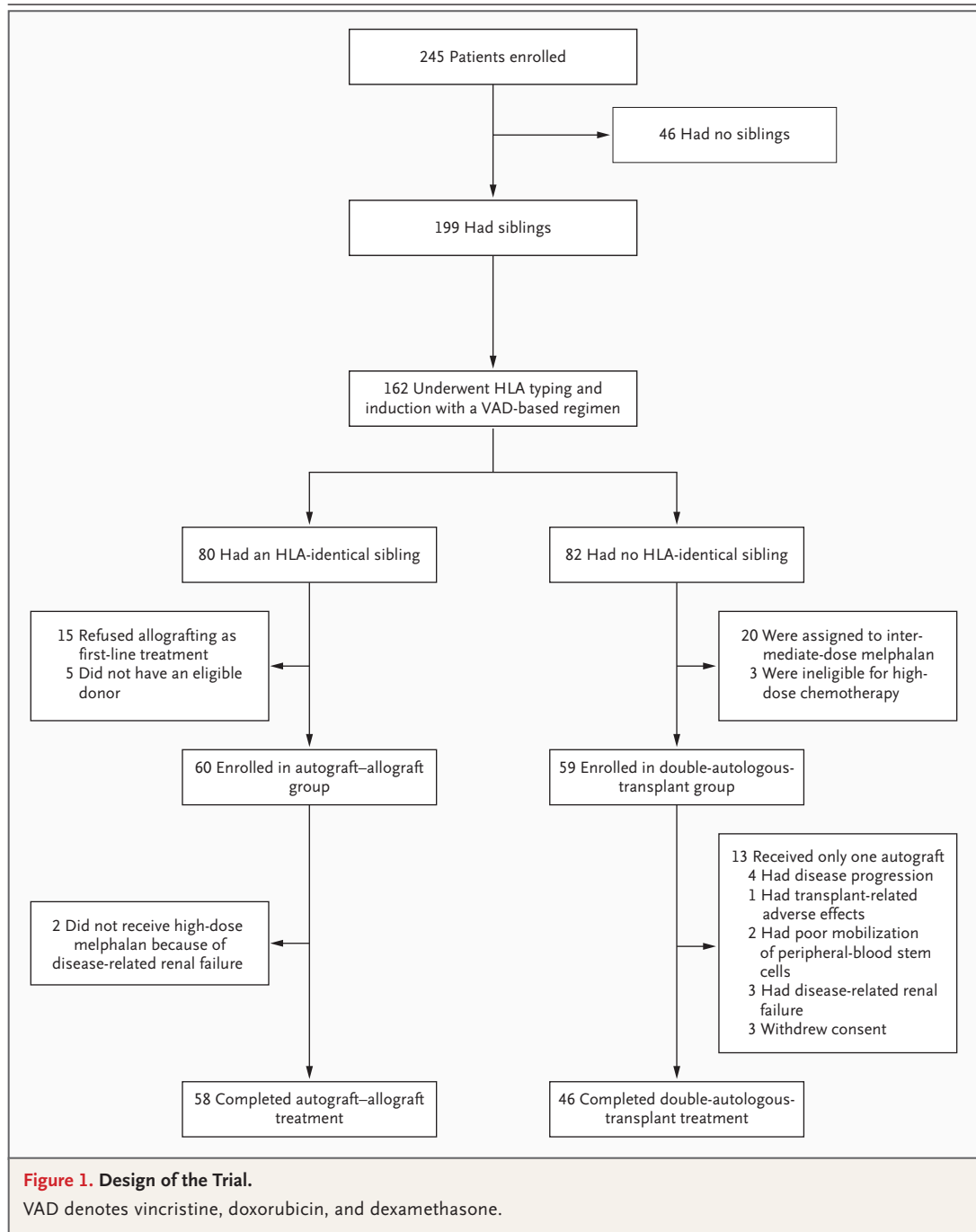
All eligible patients received induction chemotherapy consisting of two or three courses of vincristine, Adriamycin (doxorubicin), and dexamethasone (VAD). Peripheral-blood stem cells mobilized by granulocyte colony-stimulating factor (G-CSF) were collected after the patient had recovered from VAD treatment and had received 3 to 4 g of cyclophosphamide per square meter of body-sur-

face area, with or without 250 mg of paclitaxel per square meter. These cells constituted the autografts that were used in subsequent treatment. The eligibility criteria for the induction phase of VAD chemotherapy were a serum bilirubin level no higher than twice normal, serum alanine aminotransferase and aspartate aminotransferase levels no higher than four times normal, a left ventricular ejection fraction of at least 40%, a creatinine clearance of at least 40 ml per minute, and a Karnofsky performance score of at least 60%.

Patients with an HLA-identical sibling (mean age of the siblings, 54 years; range, 35 to 69) were offered the induction protocol described above followed by a standard hematopoietic stem-cell autograft, which was to be followed by a stem-cell allograft from the sibling. The autograft was to be administered after a dose of 200 mg of melphalan per square meter; the allograft was to be administered after preparation with nonmyeloablative total-body irradiation.¹¹ This group will be referred to as the autograft-allograft group.

Recovery from the initial autografting, which usually occurred 2 to 4 months after the procedure, was defined by resolution of mucositis, the absence of detectable cytomegalovirus antigen in the blood, and the absence of a need for intravenous medications. Recovered patients were prepared for allografting with a nonmyeloablative dose of 200 cGy of total-body irradiation on day 0. Hematopoietic stem cells were mobilized from the sibling's blood by administering G-CSF at a dose of 16 μ g per kilogram of body weight from day -4 to day 0, with apheresis on days -1 and 0. Both collections of nucleated cells were infused immediately after the radiotherapy (day 0). After infusion of the allogeneic cells, mycophenolate mofetil and cyclosporine were administered.¹¹ Analysis of hematopoietic chimerism was performed as previously described.¹¹ Patients who did not have graft-versus-host disease (GVHD) but who had a relapse or progression of disease after receiving the allograft were allowed to receive infusions of lymphocytes from the donor. Standard criteria were used for the diagnosis and clinical grading of acute and chronic GVHD.^{13,14}

Patients without an HLA-identical sibling and those who refused allografting or whose donor was ineligible were assigned to double autologous transplantation after receiving intermediate doses (100 mg per square meter) or high doses (140 to 200 mg per square meter) of melphalan. They re-



ceived 5 μg of G-CSF per kilogram from day 1 or 3 until neutrophil counts above 1000 per cubic millimeter were achieved. This group will be referred to as the double-autologous-transplant group.

CRITERIA FOR RESPONSE

The criteria for complete remission were the absence of detectable monoclonal immunoglobulin

in serum and of discernible light chains in urine by standard electrophoresis, the absence of visible monoclonal bands on immunofixation, less than 1% plasma cells in marrow aspirates, the absence of evidence of clonal disease according to flow cytometry of marrow cells, and the absence of an increase in the size or number of osteolytic lesions. Partial remission was defined as

a reduction of at least 75% in monoclonal immunoglobulin in serum, a reduction of at least 90% in 24-hour urinary light-chain excretion, no increase in the size or number of osteolytic lesions, and no increase in infiltration of the bone marrow by plasma cells.

The disease was considered refractory in patients with less than a partial remission after induction chemotherapy or autografting; the disease was considered stable if neither complete nor partial remission was observed after allografting. The response criteria had to be met on two occasions at least 6 weeks apart. Progressive disease was defined as an increase of at least 25% in serum monoclonal immunoglobulin or urinary light chains in patients with refractory or stable disease.

For patients in complete remission, relapse was defined as the reappearance of plasma cells in the marrow, the reappearance of monoclonal immunoglobulin in the serum or light chains in the urine, or the appearance of new bone lesions; for patients in partial remission, relapse was defined as a 25% increase in any disease marker. The patients were assessed for response before each treatment, monthly for the first 6 months after transplantation, and at least every 3 months thereafter, or as clinically indicated.

STATISTICAL ANALYSIS

The primary end points were overall survival and event-free survival from the time of diagnosis. The analyses were performed according to the intention-to-treat principle. The secondary end points included overall survival and event-free survival, disease response, and transplant-related death in patients in whom the procedure was completed. Overall survival from the date of diagnosis until the date of death from any cause was estimated according to the Kaplan–Meier method; event-free survival was estimated from the date of diagnosis until the date of disease progression, relapse, or death from any cause.¹⁵ Estimates of the incidence rates of acute and chronic GVHD and of treatment-related mortality were made according to the cumulative incidence method of Gooley et al.¹⁶ The significance of differences between curves of treatment-related mortality was assessed with Gray's test.¹⁷ Deaths not related to relapse of myeloma or to nonhematologic cancers were classified as transplant-related deaths.

Proportions were compared between groups

with the use of Fisher's exact test. To assess differences in overall survival and event-free survival, hazard ratios and corresponding 95% confidence intervals (CIs) were estimated with the use of the Cox proportional-hazards method.¹⁸ All P values in regression models were determined with the use of the Wald test. To check the assumptions of the proportional-hazards model, an interaction term between the group variable and a log function of time was included in both the overall survival and the event-free survival models; the assumptions were always satisfied. In addition to the presence or absence of an HLA-identical sibling, all multivariate models included age; sex; disease stage; serum level of β_2 -microglobulin, albumin, lactate dehydrogenase, and creatinine; platelet count at diagnosis; and the isotype of the myeloma protein. Standard prognostic factors were dichotomized in accordance with the International Staging System for multiple myeloma.¹⁹ Follow-up ended on June 1, 2006. SAS software, version 8.2, and R 2.1.0 software, package *cmprsk*, were used.

RESULTS

PATIENTS AND TREATMENT ASSIGNMENTS

Figure 1 shows the design of the trial. Table 1 shows the characteristics of the patients; 162 of 199 patients and their siblings underwent HLA typing (Fig. 1), and 80 of the 162 patients had an HLA-identical sibling. Of these 80 patients, 15 refused allografting and 5 had ineligible sibling donors; the remaining 60 were assigned to the autograft–allograft group, and 58 of them completed the protocol (Fig. 1).

The 82 patients without an HLA-identical sibling were assigned to the double-autologous-transplant group; 59 of these patients received a high dose (140 to 200 mg per square meter) of melphalan before the second autograft, and 20 received an intermediate dose (100 mg per square meter) of melphalan, as clinically indicated.²⁰ The remaining three patients were found to be ineligible after assignment. Of the 59 patients in the double-autologous-transplant group who received a high dose of melphalan, 46 completed the protocol. The outcomes of patients in the group receiving a high dose of melphalan and a double autologous transplant were compared with those of patients in the autograft–allograft group.

Table 1. Characteristics of the Patients.

Characteristic	All Patients (N=245)	Patients with HLA-Identical Siblings (N=80)	Patients without HLA-Identical Siblings (N=82)	Patients Who Completed Autograft- Allograft Treatment (N=58)	Patients Who Completed Double- Autologous- Transplant Treatment (N=46)
Male sex — no. (%)	140 (57)	41 (51)	47 (57)	30 (52)	27 (59)
Mean age — yr (range)	55 (30–65)	54 (34–65)	54 (33–65)	55 (34–65)	55 (33–63)
Durie–Salmon stage II — no. (%)*	73 (30)	22 (28)	26 (32)	13 (22)	17 (37)
Durie–Salmon stage III — no. (%)*	172 (70)†	58 (73)‡	56 (68)§	45 (78)‡	29 (63)§
IgG gammopathy — no. (%)	133 (54)	42 (52)	45 (55)	33 (57)	28 (61)
IgA gammopathy — no. (%)	50 (20)	16 (20)	19 (23)	10 (17)	6 (13)
IgM gammopathy — no. (%)	1 (<1)	—	—	—	—
Bence Jones urinary protein — no. (%)	49 (20)	17 (21)	13 (16)	11 (19)	8 (17)
Nonsecretory myeloma — no. (%)	12 (5)	5 (6)	5 (6)	4 (7)	4 (9)
β_2 -Microglobulin ≥ 3.5 mg/liter (297 nm/liter) — no./total no. (%)	76/213 (36)	27/72 (38)	23/71 (32)	20/54 (37)	11/38 (29)
Albumin < 3.5 g/dl — no./total no. (%)	42/204 (21)	20/65 (31)	9/57 (16)	14/49 (29)	4/34 (12)
Creatinine ≥ 2 mg/dl (177 μ mol/liter) — no./total no. (%)	30 (12)	11 (14)	6 (7)	7 (12)	4 (9)
Lactate dehydrogenase above normal level — no./total no. (%)	38/210 (18)	19/73 (26)	10/73 (14)	14/54 (26)	4/41 (10)
Hemoglobin < 10 g/dl — no./total no. (%)	93/239 (39)	28/78 (36)	35/82 (43)	20/58 (34)	17/46 (37)
Platelet count $< 130,000/\text{mm}^3$ — no./total no. (%)	37/235 (16)	11/76 (14)	10/80 (12)	8/57 (14)	7/45 (16)
Chromosome 13 deletion — no./total no. (%)	31/85 (36)	9/24 (38)	12/28 (43)	5/13 (38)	5/13 (38)

* In the Durie–Salmon clinical staging system for multiple myeloma, patients with stage I disease do not require immediate treatment, and patients with stage II or stage III disease have active, symptomatic myeloma.

† Progression from untreated stage I disease occurred in 11 patients.

‡ Progression from untreated stage I disease occurred in two patients.

§ Progression from untreated stage I disease occurred in one patient.

RESPONSES AND TRANSPLANT-RELATED MORTALITY

Autograft–Allograft Protocol

After receiving total-body irradiation (200 cGy), 58 of the 60 patients who were assigned to the autograft–allograft group received an infusion of allogeneic stem cells at a median of 94 days after receiving 200 mg of melphalan per square meter and an autologous hematopoietic cell transplant. Two patients in this group became ineligible after assignment because of disease-related renal failure requiring dialysis before autografting. In all 58 patients who received an allograft, complete donor hematopoietic chimerism was found by day 84.

Of the 58 patients who completed the autograft–allograft protocol, 3 were in complete remission and 29 were in partial remission at the time of allografting, whereas 8 were in complete

remission and 36 were in partial remission at the time of allografting. Of these 58 patients, 32 (55%) had a complete remission and 18 (31%) had a partial remission after allografting. At a median follow-up time of 46 months from diagnosis (range, 23 to 85) and 37 months from receipt of the allograft (range, 10 to 72), 7 of the 32 patients with a complete remission and 6 of the 18 with a partial remission had had a relapse. Overall, 11 of 58 patients (19%) received postgrafting donor lymphocyte infusions at a starting dose of 1×10^6 T cells per kilogram of body weight for relapse or progressive disease, but only 4 had a transient partial remission. Overall, 21 of 58 patients (36%) were in complete remission after a median follow-up of 38 months (range, 10 to 72) from allografting. Four patients in complete remission died of transplant-related causes.

Acute grade II, III, or IV GVHD developed in 25 of the 58 patients at a median of 40 days (range, 22 to 115) after allografting. Two of these patients had grade IV disease. The cumulative incidence rates for grade II, III, and IV GVHD and for grade IV GVHD were 43% and 4%, respectively (Fig. 2A). Extensive chronic GVHD developed in 21 patients, with a cumulative incidence of 32% at 2 years (Fig. 2B). Chronic GVHD developed in 22 of 32 patients in complete remission and in 15 of 26 patients who were not in complete remission. There was no association between the clinical response to therapy and either acute GVHD ($P=0.72$) or chronic GVHD ($P=0.44$). Thirty-six of 50 patients were receiving immunosuppressive therapy at 1 year after allografting, 19 of 36 at 2 years, and 5 of 10 at 4 years. Most

of these patients had a Karnofsky performance score of 90 to 100.

Twelve of the 58 patients died: 4 from disease progression, 6 from transplant-related causes, and 2 from lung cancer. Transplant-related death was due to progressive encephalopathy (one patient), complications associated with grade IV acute or chronic GVHD (four patients), and the hemolytic-uremic syndrome (or thrombotic thrombocytopenic purpura) (one patient). The cumulative incidence of treatment-related death at 2 years was 10% (Fig. 2C).

Double-Autologous-Transplant Protocol

All 59 patients in the group assigned to receive a high dose of melphalan and a double autologous transplant received the first autologous transplant,

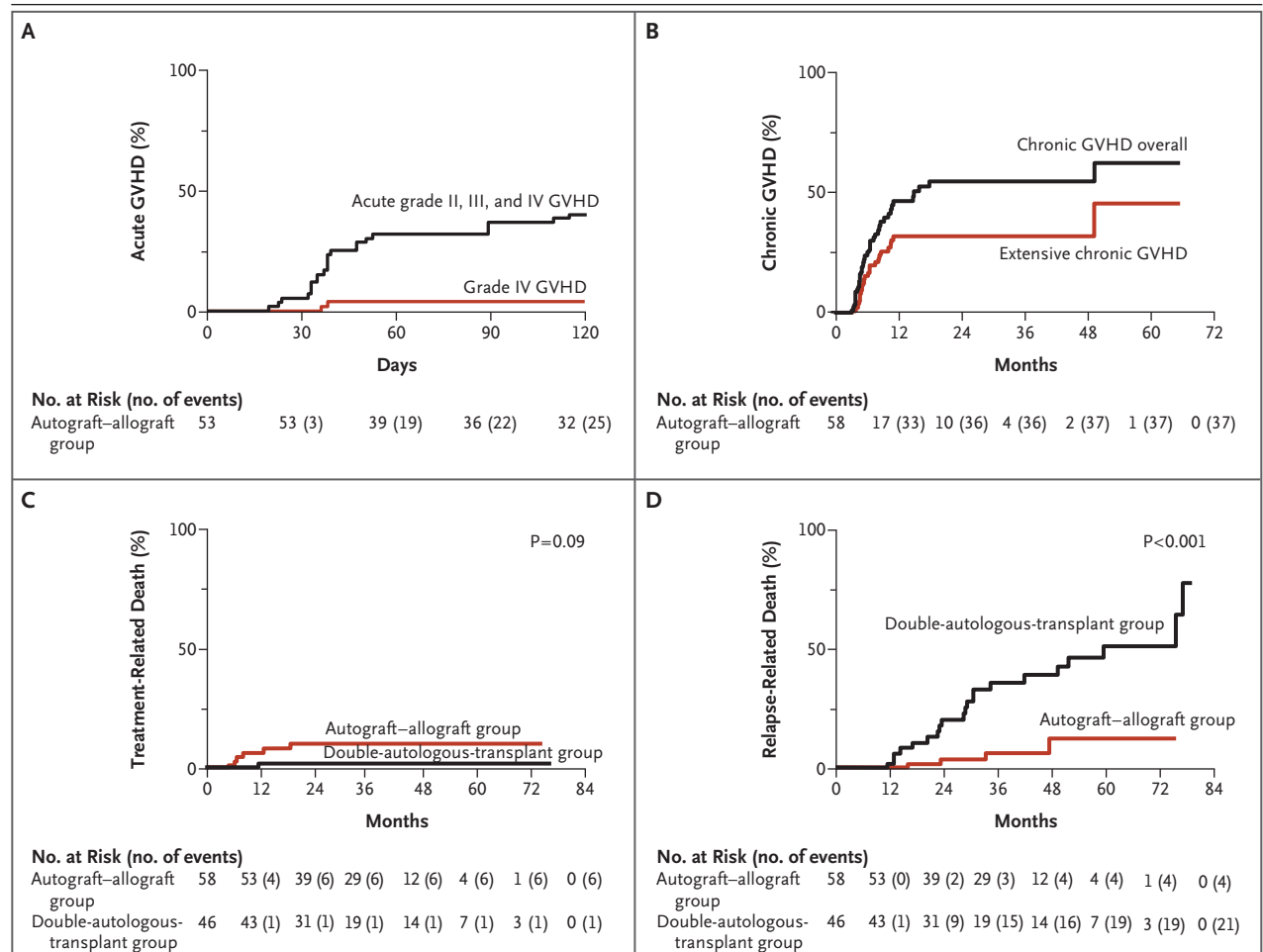


Figure 2. Estimates of Cumulative Incidence Rates.

Panel A shows the results for acute graft-versus-host disease (GVHD), and Panel B for chronic GVHD. Panel C shows treatment-related mortality, and Panel D shows relapse-related mortality calculated from the first autograft.

but only 46 received the second (at a median of 123 days after the first transplant). Of the 13 patients who received only the first transplant, 4 had disease progression, 3 had disease-related renal failure, 1 had transplant-related adverse effects, 3 withdrew consent, and 2 had poor mobilization of peripheral-blood stem cells.

Of the 46 patients who received two autografts, 1 had entered a complete remission and 22 had entered a partial remission after the induction chemotherapy that was given before the first autograft. Before receiving the second autograft, 4 patients were in complete remission and 31 were in partial remission. Eleven patients had refractory disease. After the second transplant, 12 patients (26%) had a complete remission and 29 (63%) had a partial remission. At a median follow-up time of 53 months from diagnosis (range, 21 to 88) and 36 months from the second transplant (range, 15 to 69), 27 patients had had a relapse from a previous complete or partial remission, and only 4 were in complete remission.

Twenty-five of the 46 patients died: 21 from disease progression, 1 from transplant-related invasive aspergillosis, 1 from gallbladder cancer, and 2 from complications during salvage treatments. The cumulative incidence of treatment-related mortality at 2 years was 2% (Fig. 2C).

The overall response rates (complete remission plus partial remission) after induction chemotherapy and after the first autograft did not differ significantly between the two groups ($P=0.74$ and $P=0.83$, respectively). However, the rate of complete remission was significantly higher in the autograft–allograft group than in the double-autologous-transplant group (55% vs. 26%, $P=0.004$). The two groups did not differ significantly with respect to treatment-related mortality after a median follow-up of 45 months ($P=0.09$), but disease-related mortality was significantly higher in the double-autologous-transplant group than in the autograft–allograft group (43% vs. 7%, $P<0.001$) (Fig. 2D).

SURVIVAL

On June 1, 2006, at a median follow-up period of 45 months (range, 21 to 90), the median overall survival for all 245 patients was 63 months, and there were no significant differences in overall survival between the 162 HLA-typed patients, the 37 non-HLA-typed patients, and the 46 patients without siblings ($P=0.98$) (Fig. 3A and 3B). Prog-

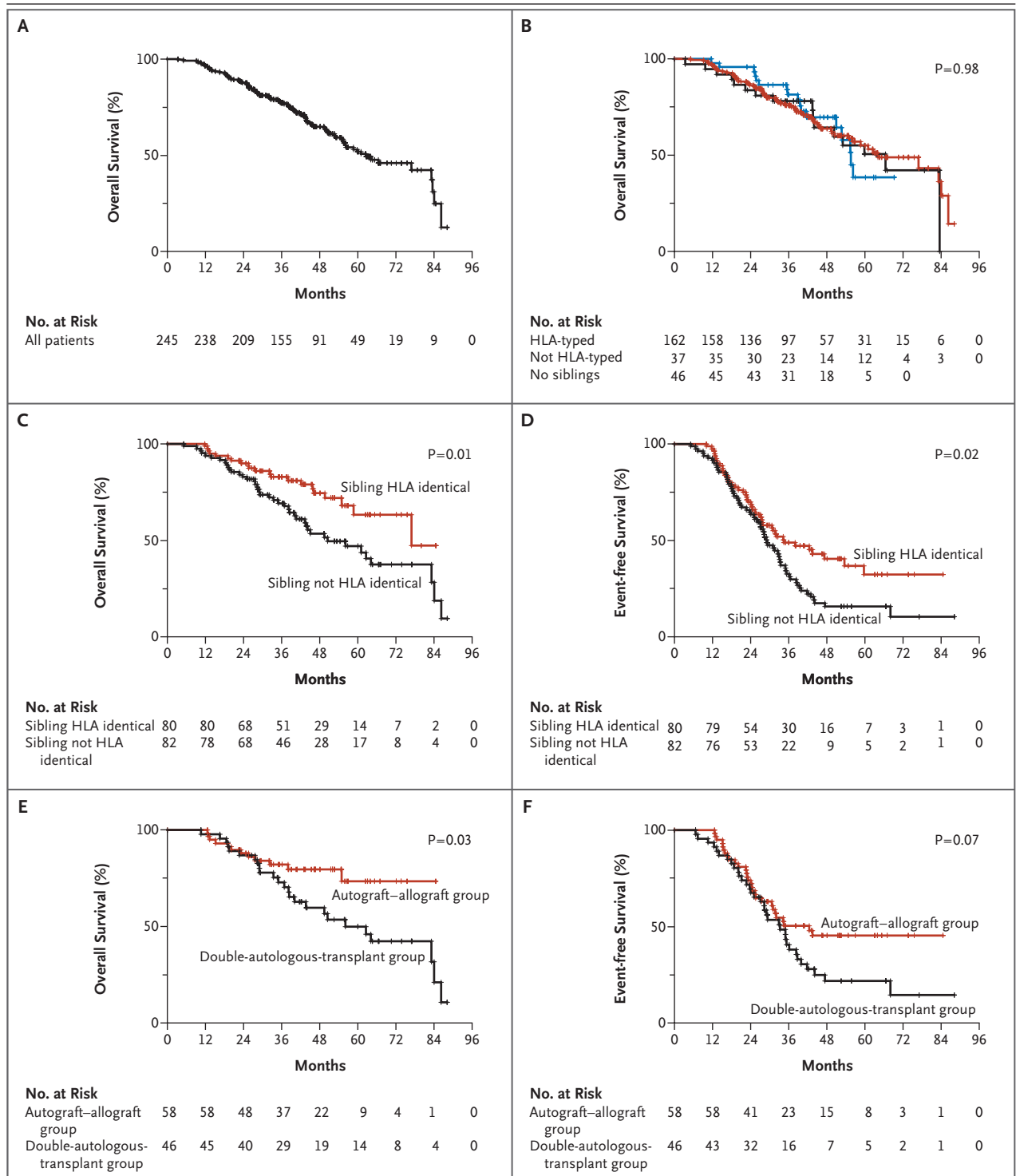
Figure 3 (facing page). Kaplan–Meier Estimates of Overall and Event-free Survival from Time of Diagnosis.

Panel A shows the overall survival of 245 consecutive patients receiving a diagnosis of stage II or III multiple myeloma from September 1998 through July 2004. Panel B shows the overall survival of 199 patients with siblings (the red line indicates the 162 patients who underwent HLA typing, and the black line the 37 patients who did not undergo HLA typing) and 46 patients without siblings (blue line). Panel C shows the overall survival and Panel D the event-free survival of the 80 patients with an HLA-identical sibling and the 82 patients without an HLA-identical sibling according to intention-to-treat analysis. Panel E shows the overall survival and Panel F the event-free survival of the 58 patients who completed the autograft–allograft protocol and the 46 patients who completed the high-dose-melphalan, double-autologous-transplant protocol. All P values are for univariate comparisons with Cox models.

nostic factors were evenly distributed in all groups (Table 1).

MULTIVARIATE ANALYSIS

Table 2 and Figures 3C and 3D show that, according to intention-to-treat analyses, median overall survival and event-free survival were significantly longer in patients with an HLA-identical sibling, regardless of the treatment received, than in patients without such a sibling: 80 versus 54 months (hazard ratio, 0.51; 95% CI, 0.30 to 0.86; $P=0.01$) and 35 versus 29 months (hazard ratio, 0.63; 95% CI, 0.43 to 0.92; $P=0.02$), respectively. Univariate and multivariate analyses of overall and event-free survival in all 162 patients with a sibling and the 104 patients who completed their assigned protocols included as variables age; sex; serum levels of β_2 -microglobulin, albumin, lactate dehydrogenase, and creatinine; platelet count; and the isotype of the myeloma protein (Table 2). The availability of an HLA-identical sibling and, therefore, the possibility of receiving an allograft were significantly associated with longer overall survival (hazard ratio, 0.35; 95% CI, 0.19 to 0.64; $P=0.001$) and event-free survival (hazard ratio, 0.54; 95% CI, 0.35 to 0.81; $P=0.003$) (Table 2). In a stratified analysis that classified patients with high β_2 -microglobulin levels or with chromosome 13 abnormalities as being at high risk, the adjusted hazard ratios were 0.34 (95% CI, 0.10 to 1.18) for overall survival and 0.52 (95% CI, 0.22 to 1.21) for event-free survival; these ratios were similar to those for all 162 patients combined.



OUTCOMES

At a median follow-up of 46 months (range, 22 to 88), the median overall survival had not been reached in the group of 58 patients who had completed the autograft-allograft protocol and was

58 months in the 46 who had completed the double-autologous-transplant protocol (hazard ratio, 0.46; 95% CI, 0.23 to 0.93; $P=0.03$) (Fig. 3E). Event-free survival was 43 and 33 months, respectively, in the two groups (hazard ratio, 0.63; 95% CI, 0.39

Table 2. Univariate and Multivariate Analysis (Cox Models) of Overall and Event-free Survival in 162 HLA-Typed Patients and 104 Patients Who Completed Their Protocols.*

Variable	Overall Survival			Event-free Survival			
	Univariate Analysis hazard ratio (95% CI)	P value	hazard ratio (95% CI)	Univariate Analysis hazard ratio (95% CI)	P value	Multivariate Analysis hazard ratio (95% CI)	P value
162 HLA-typed patients							
HLA-identical sibling							
Not present	1	—	1	1	—	1	—
Present	0.51 (0.30–0.86)	0.01	0.35 (0.19–0.64)	0.63 (0.43–0.92)	0.001	0.54 (0.35–0.81)	0.003
Male sex	1.26 (0.76–2.08)	0.37	1.06 (0.61–1.84)	0.97 (0.66–1.40)	0.82	0.99 (0.66–1.48)	0.95
Age	1.02 (0.98–1.06)	0.22	1.04 (0.10–1.09)	1.04 (1.01–1.07)	0.06	1.05 (1.02–1.09)	0.003
IgG myeloma	0.77 (0.47–1.26)	0.30	0.71 (0.41–1.21)	0.73 (0.50–1.07)	0.21	0.74 (0.49–1.11)	0.15
Durie–Salmon stage III†	1.12 (0.66–1.91)	0.67	1.09 (0.62–1.91)	1.08 (0.72–1.62)	0.75	1.03 (0.68–1.56)	0.89
Creatinine ≥ 2 mg/dl	0.90 (0.39–2.08)	0.81	0.76 (0.29–1.99)	0.57 (0.28–1.17)	0.58	0.48 (0.22–1.04)	0.06
β_2 -Microglobulin ≥ 3.5 mg/liter‡	1.70 (0.99–2.90)	0.05	1.21 (0.66–2.21)	1.54 (1.03–2.31)	0.53	1.44 (0.90–2.29)	0.12
Albumin < 3.5 g/dl‡	1.47 (0.71–3.05)	0.30	1.74 (0.80–3.80)	0.73 (0.42–1.28)	0.16	0.79 (0.43–1.46)	0.45
Lactate dehydrogenase above normal level‡	2.45 (1.33–4.50)	0.004	3.93 (1.99–7.76)	2.32 (1.46–3.70)	< 0.001	3.17 (1.90–5.31)	< 0.001
Platelet count $< 130,000/\text{mm}^3$	2.30 (1.24–4.25)	0.008	3.58 (1.74–7.36)	2.07 (1.22–3.51)	0.001	3.31 (1.80–6.08)	< 0.001
104 Patients who completed protocols							
Double-autologous transplant	1	—	1	1	—	1	—
Autograft–allograft	0.46 (0.23–0.93)	0.03	0.33 (0.14–0.80)	0.63 (0.39–1.04)	0.01	0.47 (0.27–0.83)	0.009

* In both populations, multivariate hazard ratios were adjusted for sex; age (as a continuous variable); myeloma protein isotype (IgG vs. others); Durie–Salmon stage (III vs. I or II); serum levels of creatinine (≥ 2 mg per deciliter vs. < 2 mg per deciliter [≥ 177 μmol per liter vs. < 177 μmol per liter]), β_2 -microglobulin (≥ 3.5 mg per liter vs. < 3.5 mg per liter [≥ 297 nmol per liter vs. < 297 nmol per liter]), albumin (< 3.5 g per deciliter), and lactate dehydrogenase (above normal level vs. at or below normal level); and platelet count ($< 130,000$ vs. $\geq 130,000$ per cubic millimeter).

† In the Durie–Salmon clinical staging system for multiple myeloma, patients with stage I disease do not require immediate treatment, and patients with stage II or stage III disease have active, symptomatic myeloma.

‡ Patients with unknown values were included in the analyses by using dummy variables indicating missing data.

to 1.04; $P=0.07$) (Fig. 3F). Multivariate analysis of all 104 patients who completed a hematopoietic stem-cell grafting procedure showed that patients who received a hematopoietic stem-cell graft from an HLA-identical sibling donor had significantly longer overall survival (hazard ratio, 0.33; 95% CI, 0.14 to 0.80; $P=0.01$) and event-free survival (hazard ratio, 0.47; 95% CI, 0.27 to 0.83; $P=0.009$) than patients who underwent the high-dose-melphalan, double-autologous-transplant procedure (Table 2).

DISCUSSION

We investigated a protocol for the treatment of multiple myeloma that began with VAD chemotherapy followed by melphalan, with rescue of the hematopoietic system by an autologous stem-cell transplant. After recovering from the autologous stem-cell transplantation, patients with an HLA-identical sibling received total-body irradiation with rescue of the marrow by allogeneic hematopoietic stem cells from the sibling. The outcome of this three-part procedure was compared with that of a protocol in patients who lacked an HLA-identical sibling, in which the patient first received the same VAD chemotherapy and underwent the same first autologous-transplant procedure but then received a high dose of melphalan and a second autologous transplant. Overall survival and event-free survival were significantly longer in the first group than in the second group ($P=0.001$ and $P=0.003$, respectively). The novel feature of this study is the assignment of treatment according to a single criterion: the presence or absence of an HLA-identical sibling donor. This type of genetic randomization has been applied to the assessment of outcomes in patients with hematologic disorders who were treated with allografting or other therapies.²¹⁻²⁴ A comparison by the intention-to-treat principle of outcomes in consecutive patients who were enrolled in the study on the sole criterion of having a sibling, either HLA-identical or not, is a surrogate for an unbiased randomization.

The median overall survival of all 245 patients who were enrolled in this study was more than 5 years. Overall survival and event-free survival were significantly longer ($P=0.01$ and $P=0.009$, respectively) in patients who completed the autograft-allograft protocol than in patients who completed the high-dose, double-autograft pro-

ocol. Nineteen percent of the eligible patients refused the autograft-allograft protocol, mostly because of concerns about the high transplant-related mortality previously reported for myeloablative conditioning.⁶⁻⁹

High-dose melphalan with rescue by autologous stem cells has become the standard treatment for young patients with myeloma.¹⁻⁴ However, eradication of all malignant cells by this procedure is problematic. The curative potential of hematopoietic allografts presumably relies on an immune attack of donor cells against myeloma cells.²⁵⁻²⁷ In the Intergroup Trial S9321,²⁸ the study design included myeloablative allografting for patients 55 years of age or younger with a suitable sibling donor. The treatment option was discontinued early in this group of patients because of a transplant-related mortality rate of 53%. However, 22% of the patients in this group were alive and free of disease progression 7 years after allografting.

In our study, the frequency of deaths that were unrelated to relapse was low in both groups; GVHD and its complications accounted for most treatment-related mortality in the autograft-allograft group. A regimen of total lymphoid irradiation (800 cGy total) plus antithymocyte globulin can decrease the incidence of GVHD after allogeneic stem-cell transplantation to 3% without impairing graft-versus-tumor activity.²⁹ This immunosuppressive protocol may cause a greater reduction in the alloreactivity of donor CD4+ T cells than would a single dose of total-body irradiation (200 cGy).

With a maximal follow-up period of 7 years, we have seen only seven relapses among 32 patients in complete remission. There was no correlation between complete remission and the development of chronic GVHD. This phenomenon may be due to the nonmyeloablative conditioning, which does not favor GVHD yet allows a graft-versus-myeloma effect.

Comparison of our results with the outcomes of other reduced-intensity conditioning protocols is difficult, since the preparative regimen and the intensity of immune suppression after allografting are pivotal in treating myeloma. Garban et al. did not find an advantage of allografting over melphalan-based autografting in patients with high-risk myeloma (i.e., those with an elevated β_2 -microglobulin level plus chromosome 13 abnormalities).³⁰ This study, unlike ours, did not

enroll patients who were at intermediate or good risk, nor were additional prognostic factors evaluated by intention-to-treat analysis. Furthermore, the potent pretransplantation immune suppression with antithymocyte globulin used in the study of Garban et al. may have prevented graft-versus-myeloma effects. In our study, neither chromosome 13 abnormalities nor β_2 -microglobulin levels appeared to affect the outcome after allografting.

Supported in part by Progetti di Ricerca ex-60% (Ministero dell'Università e della Ricerca Scientifica); Regione Piemonte Ricerca Finalizzata 2005 (Progetto Clinico-scientifico e di Coordinamento Regionale); Compagnia di San Paolo; Fondazione Cassa di Risparmio di Torino and Comitato Regionale Piemontese Gigi Ghirotti (Progetto Vita Vitae); Fondazione Neoplasie Sangue Onlus; and a grant (CA78902) from the National Cancer Institute.

No potential conflict of interest relevant to this article was reported.

We thank the nurses and medical staff for caring for the patients, the data coordinators for collecting the study and follow-up information, and Dr. John Iliffe for his critical reading of the manuscript and thoughtful suggestions.

REFERENCES

- Attal M, Harousseau J-L, Stoppa A-M, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. *N Engl J Med* 1996;335:91-7.
- Child JA, Morgan GJ, Davies FE, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. *N Engl J Med* 2003;348:1875-83.
- Attal M, Harousseau JL, Facon T, et al. Single versus double autologous stem-cell transplantation for multiple myeloma. *N Engl J Med* 2003;349:2495-502. [Erratum, *N Engl J Med* 2004;350:2628.]
- Barlogie B, Tricot GJ, van Rhee F, et al. Long-term outcome results of the first tandem autotransplant trial for multiple myeloma. *Br J Haematol* 2006;135:158-64.
- Corradini P, Voena C, Tarella C, et al. Molecular and clinical remissions in multiple myeloma: role of autologous and allogeneic transplantation of hematopoietic cells. *J Clin Oncol* 1999;17:208-15.
- Gahrton G, Tura S, Ljungman P, et al. Allogeneic bone marrow transplantation in multiple myeloma. *N Engl J Med* 1991;325:1267-73.
- Gahrton G, Tura S, Ljungman P, et al. Prognostic factors in allogeneic bone marrow transplantation for multiple myeloma. *J Clin Oncol* 1995;13:1312-22.
- Bensinger WI, Buckner CD, Anasetti C, et al. Allogeneic marrow transplantation for multiple myeloma: an analysis of risk factors on outcome. *Blood* 1996;88:2787-93.
- Gahrton G, Svensson H, Cavo M, et al. Progress in allogeneic bone marrow and peripheral blood stem cell transplantation for multiple myeloma: a comparison between transplants performed 1983-93 and 1994-8 at European Group for Blood and Marrow Transplantation centres. *Br J Haematol* 2001;113:209-16.
- Kroger N, Schwerdtfeger R, Kiehl M, et al. Autologous stem cell transplantation followed by a dose-reduced allograft induces high complete remission rate in multiple myeloma. *Blood* 2002;100:755-60.
- Maloney DG, Molina AJ, Sahebi F, et al. Allografting with nonmyeloablative conditioning following cytoreductive autografts for the treatment of patients with multiple myeloma. *Blood* 2003;102:3447-54.
- Kyle RA, Rajkumar SV. Multiple myeloma. *N Engl J Med* 2004;351:1860-73. [Erratum, *N Engl J Med* 2005;352:1163.]
- Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus Conference on Acute GVHD Grading. *Bone Marrow Transplant* 1995;15:825-8.
- Sullivan KM, Agura E, Anasetti C, et al. Chronic graft-versus-host disease and other late complications of bone marrow transplantation. *Semin Hematol* 1991;28:250-9.
- Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457-81.
- Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. *Stat Med* 1999;18:695-706.
- Gray RJ. A class of k-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat* 1988;16:1141-54.
- Cox DR. Regression models and life-tables. *J R Stat Soc [B]* 1972;34:187-220.
- Greipp PR, San Miguel J, Durie BG, et al. International Staging System for multiple myeloma. *J Clin Oncol* 2005;23:3412-20. [Erratum, *J Clin Oncol* 2005;23:6281.]
- Palumbo A, Bringhen S, Petrucci MT, et al. Intermediate-dose melphalan improves survival of myeloma patients aged 50 to 70: results of a randomized controlled trial. *Blood* 2004;104:3052-7.
- Wheatley K, Gray R. Mendelian randomization — an update on its use to evaluate allogeneic stem cell transplantation in leukaemia. *Int J Epidemiol* 2004;33:15-7.
- Balduzzi A, Valsecchi MG, Uderzo C, et al. Chemotherapy versus allogeneic transplantation for very-high-risk childhood acute lymphoblastic leukaemia in first complete remission: comparison by genetic randomisation in an international prospective study. *Lancet* 2005;366:635-42.
- Woods WG, Neudorf S, Gold S, et al. A comparison of allogeneic bone marrow transplantation, autologous bone marrow transplantation, and aggressive chemotherapy in children with acute myeloid leukemia in remission. *Blood* 2001;97:56-62.
- Suciu S, Mandelli F, de Witte T, et al. Allogeneic compared with autologous stem cell transplantation in the treatment of patients younger than 46 years with acute myeloid leukemia (AML) in first complete remission (CR1): an intention-to-treat analysis of the EORTC/GIMEMAAML-10 trial. *Blood* 2003;102:1232-40.
- Aschan J, Lonnqvist B, Ringden O, Kumlien G, Gahrton G. Graft-versus-myeloma effect. *Lancet* 1996;348:346.
- Tricot G, Vesole DH, Jagannath S, Hilton J, Munshi N, Barlogie B. Graft-versus-myeloma effect: proof of principle. *Blood* 1996;87:1196-8.
- Le Blanc R, Montminy-Métivier S, Bélanger R, et al. Allogeneic transplantation for multiple myeloma: further evidence for a GVHD-associated graft-versus-myeloma effect. *Bone Marrow Transplant* 2001;28:841-8.
- Barlogie B, Kyle RA, Anderson KC, et al. Standard chemotherapy compared with high-dose chemoradiotherapy for multiple myeloma: final results of phase III US Intergroup Trial S9321. *J Clin Oncol* 2006;24:929-36. [Erratum, *J Clin Oncol* 2006;24:2687.]
- Lowsky R, Takahashi T, Liu YP, et al. Protective conditioning for acute graft-versus-host disease. *N Engl J Med* 2005;353:1321-31. [Erratum, *N Engl J Med* 2006;354:884.]
- Garban F, Attal M, Michallet M, et al. Prospective comparison of autologous stem cell transplantation followed by dose-reduced allograft (IFM99-03 trial) with tandem autologous stem cell transplantation (IFM99-04 trial) in high-risk de novo multiple myeloma. *Blood* 2006;107:3474-80.

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