The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 4, 2014 VOL. 371 NO. 10

Autologous Transplantation and Maintenance Therapy in Multiple Myeloma

A. Palumbo, F. Cavallo, F. Gay, F. Di Raimondo, D.B. Yehuda, M.T. Petrucci, S. Pezzatti, T. Caravita, C. Cerrato, E. Ribakovsky, M. Genuardi, A. Cafro, M. Marcatti, L. Catalano, M. Offidani, A.M. Carella, E. Zamagni, F. Patriarca, P. Musto, A. Evangelista, G. Ciccone, P. Omedé, C. Crippa, P. Corradini, A. Nagler, M. Boccadoro, and M. Cavo

ABSTRACT

BACKGROUND

This open-label, randomized, phase 3 study compared melphalan at a dose of 200 mg per square meter of body-surface area plus autologous stem-cell transplantation with melphalan–prednisone–lenalidomide (MPR) and compared lenalidomide maintenance therapy with no maintenance therapy in patients with newly diagnosed multiple myeloma.

METHODS

We randomly assigned 273 patients 65 years of age or younger to high-dose melphalan plus stem-cell transplantation or MPR consolidation therapy after induction, and 251 patients to lenalidomide maintenance therapy or no maintenance therapy. The primary end point was progression-free survival.

RESULTS

The median follow-up period was 51.2 months. Both progression-free and overall survival were significantly longer with high-dose melphalan plus stem-cell transplantation than with MPR (median progression-free survival, 43.0 months vs. 22.4 months; hazard ratio for progression or death, 0.44; 95% confidence interval [CI], 0.32 to 0.61; P<0.001; and 4-year overall survival, 81.6% vs. 65.3%; hazard ratio for death, 0.55; 95% CI, 0.32 to 0.93; P=0.02). Median progression-free survival was significantly longer with lenalidomide maintenance than with no maintenance (41.9 months vs. 21.6 months; hazard ratio for progression or death, 0.47; 95% CI, 0.33 to 0.65; P<0.001), but 3-year overall survival was not significantly prolonged (88.0% vs. 79.2%; hazard ratio for death, 0.64; 95% CI, 0.36 to 1.15; P=0.14). Grade 3 or 4 neutropenia was significantly more frequent with high-dose melphalan than with MPR (94.3% vs. 51.5%), as were gastrointestinal adverse events (18.4% vs. 0%) and infections (16.3% vs. 0.8%); neutropenia and dermatologic toxic effects were more frequent with lenalidomide maintenance than with no maintenance (23.3% vs. 0% and 4.3% vs. 0%, respectively).

CONCLUSIONS

Consolidation therapy with high-dose melphalan plus stem-cell transplantation, as compared with MPR, significantly prolonged progression-free and overall survival among patients with multiple myeloma who were 65 years of age or younger. Lenalidomide maintenance, as compared with no maintenance, significantly prolonged progression-free survival. (Funded by Celgene; ClinicalTrials.gov number, NCT00551928.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Palumbo at the Department of Hematology, University of Turin, Via Genova 3, 10126 Turin, Italy, or at appalumbo@yahoo.com.

N Engl J Med 2014;371:895-905.
DOI: 10.1056/NEJMoa1402888

High-dose chemotherapy plus autologous stem-cell transplantation, as compared with conventional chemotherapy, prolongs progression-free survival and overall survival among patients with newly diagnosed multiple myeloma.[1-4] and it is currently the standard of care for patients who are younger than 65 years of age. However, since autologous stem-cell transplantation has substantial toxic effects and requires prolonged hospitalization, the comparison with less toxic, orally administered treatments is important. Immunomodulatory drugs and proteasome inhibitors have significantly improved outcomes in patients, regardless of whether they are eligible for transplantation.[5-18] These improvements have raised questions about the role of transplantation in comparison with conventional chemotherapy and about the timing of transplantation, since the survival benefit has not been clearly established.

Continuous treatment with immunomodulatory drugs and proteasome inhibitors has shown clinical efficacy.[19] In three large, randomized studies, continuous therapy with lenalidomide, as compared with placebo, significantly reduced the risk of disease progression (hazard ratio, 0.34 to 0.50), but the survival advantage was inconsistent.[16-18] It is currently not clear whether maintenance therapy after combination therapy will have the same effect that it does after transplantation. To address these issues, we conducted a phase 3 study to assess the efficacy and safety of melphalan at a dose of 200 mg per square meter of body-surface area (high-dose melphalan) plus stem-cell transplantation as compared with melphalan–prednisone–lenalidomide (MPR), followed by lenalidomide as maintenance therapy as compared with no maintenance therapy, in patients with newly diagnosed multiple myeloma who were eligible for transplantation.

Methods

Patients

Patients with symptomatic, measurable, newly diagnosed multiple myeloma who were 65 years of age or younger were eligible for this trial. Other inclusion criteria were a Karnofsky performance-status score of at least 60% (on a scale from 0 to 100%, with lower scores indicating greater disability) and life expectancy longer than 6 months, an absolute neutrophil count greater than 1500 per cubic millimeter[3] and a platelet count greater than 75,000 per cubic millimeter,[3] and normal cardiac and pulmonary-function findings and adequate renal function (creatinine clearance ≥30 ml per minute). The main exclusion criteria included a history of other cancers within the past 3 years and peripheral neuropathy of grade 2 or higher. The study was approved by the institutional review boards of the participating centers and was conducted according to the Declaration of Helsinki and the International Conference on Harmonisation Guidelines for Good Clinical Practice. All patients provided written informed consent.

Study Design and Oversight

The study was a randomized, open-label trial with a 2-by-2 factorial design. We recruited patients from November 2007 through July 2009 at 62 centers in Italy and Israel. A simple randomization sequence, stratified according to International Staging System disease stage[20] (stage I or II vs. stage III, with higher stages indicating more severe disease) and age (≤60 years vs. 61 to 65 years), was generated by a computer program and implemented by means of a Web-based procedure. All patients were randomly assigned (in a 1:1:1:1 ratio) at enrollment to one of the four groups, but the results of the random assignment were concealed until patients reached the end of the induction period and their eligibility for the consolidation and maintenance regimens was confirmed.

The study was designed by the senior academic authors. The sponsor, Fondazione Neoplasie Sangue Onlus, collected the data and, in collaboration with the senior academic authors, conducted the data analyses. Celgene provided an unrestricted grant to conduct the trial but was not involved in the data collection, analysis, or the writing of the manuscript. The first draft of the manuscript was developed by the first author; subsequent drafts were revised by the first three authors. A medical writer paid by Celgene provided assistance with the writing of the manuscript to improve clarity and consistency. All authors had full access to the primary data and results of the final analysis, were responsible for the content of the manuscript and the decision to submit it for publication, and vouch for the accuracy and completeness of the data and the fidelity of the study to the protocol. The protocol and statistical analysis plan are available with the full text of this article at NEJM.org.

STUDY TREATMENTS

All patients received induction therapy consisting of four 28-day cycles of lenalidomide (at a dose of 25 mg daily on days 1 through 21) plus dexamethasone (40 mg daily on days 1, 8, 15, and 22). Cyclophosphamide and granulocyte colony-stimulating factor were used to mobilize stem cells.[21] The consolidation regimen consisted of six 28-day cycles of melphalan (at a dose of 0.18 mg per kilogram of body weight on days 1 through 4), prednisone (2 mg per kilogram on days 1 through 4), and lenalidomide (10 mg on days 1 through 21), or two 4-month cycles of melphalan at a dose of 200 mg per square meter of body-surface area followed by autologous stem-cell transplantation. Patients in whom progressive disease developed during induction or consolidation therapy were treated according to local standards and remained in the trial for later outcome evaluations. Maintenance therapy was initiated within the first 3 months after completion of consolidation therapy. Maintenance therapy with lenalidomide (10 mg on days 1 through 21 of each 28-day cycle) was administered until disease progression or the development of unacceptable adverse effects. Details of dose reductions, drug discontinuations, and treatment schedules are provided in Table S1 in the Supplementary Appendix, available at NEJM.org. Details of the anticoagulation regimen used have been published previously.[22]

END POINTS AND ASSESSMENTS

The primary study end point was progression-free survival. Secondary end points included overall survival, the overall response rate, the time to a response, and safety. Time-to-event end points were estimated from the time of enrollment (for all patients) and from the time when the random assignment was disclosed (for the patients who underwent randomization). Progression-free survival was calculated until the date of disease progression, death from any cause during treatment, or data censoring at the last date on which the patient was known to be free of disease progression. Overall survival was calculated until the date of either death from any cause or data censoring at the last date on which the patient was known to be alive. Response was assessed with the use of the International Uniform Response Criteria for Multiple Myeloma.[23] Bone marrow samples were collected at enrollment and analyzed by central laboratories within each country. These samples were tested for chromosome deletions 13 and 17 and for the t(4:14) and t(14:16) translocations with the use of fluorescence in situ hybridization. No prospective decisions regarding therapy were based on the results. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).[24]

STATISTICAL ANALYSIS

The primary comparison was between high-dose melphalan with stem-cell transplantation and MPR. With a two-sided alpha error of 0.05, we estimated that 400 patients (200 per treatment group) would need to be enrolled for the study to have a statistical power of 85% to detect a hazard ratio of 0.62 in favor of high-dose melphalan versus MPR (corresponding to a 2-year progression-free survival of 65% vs. 50%), assuming 2 years of accrual, a minimum follow-up time of 1 year, and a dropout rate of 5%. The secondary comparison was between lenalidomide maintenance therapy and no maintenance therapy. We expected that approximately 240 patients (120 per treatment group) would be eligible for a maintenance regimen after consolidation treatment. With a two-sided alpha error of 0.05, this sample size had a statistical power of 80% to detect an improvement from 60% to 75% in 2-year progression-free survival in favor of the maintenance group (corresponding to a hazard ratio of 0.56).

To estimate the effect of the complete treatment strategy (induction, consolidation, and maintenance phases), both progression-free survival and overall survival were estimated for the four groups from the date of study enrollment, in an analysis that included all enrolled patients. All comparative analyses were performed with an intention-to-treat approach for the two randomized populations: the consolidation-phase population, which comprised all patients who were eligible to receive high-dose melphalan or MPR (the starting time of the analyses was the date of disclosure of randomization), and the maintenance-phase population, which comprised all patients who were eligible to receive lenalidomide maintenance therapy or no maintenance therapy (the starting time of the analyses was the date of clinical evaluation after the consolidation phase). Two interim analyses, according to the O'Brien–Fleming design, were specified

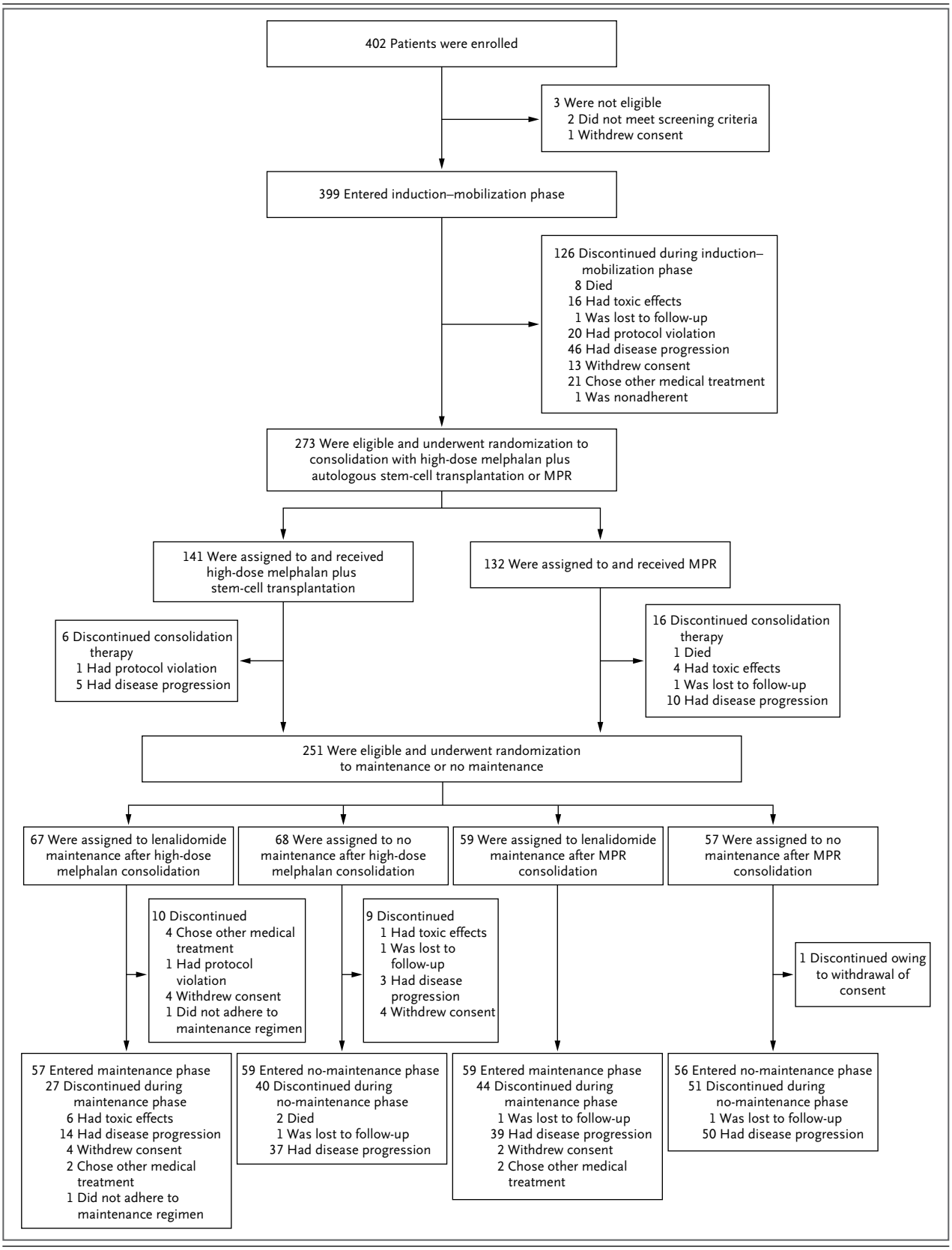


Figure 1 (facing page). Randomization, Treatment, and Follow-up of the Enrolled Patients.
MPR denotes melphalan–prednisone–lenalidomide.

by the protocol for the comparison of high-dose melphalan with MPR: the first when 65 progression events (40% of the expected number) had occurred, and the second when 97 events (60% of the expected number) had occurred; the study was completed as originally planned.

The safety-analysis population included all patients who received at least one dose of the study treatments. Response and safety data were compared among the treatment groups by means of the chi-square test or Fisher's exact test, as appropriate. Time-to-event data were analyzed with the use of the Kaplan–Meier method, and the groups were compared with the use of the log-rank test. Cox proportional-hazards models were used to estimate hazard ratios and 95% confidence intervals for the main comparisons. Cox models, adjusted for age and International Staging System stage, were also used to explore any modification of the effect of consolidation or maintenance therapy between subgroups (including the subgroups that were prespecified according to age and disease stage), with the use of interaction terms. Between-group differences in patient characteristics were evaluated with the use of the Mann–Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables, as appropriate. Statistical analyses were performed with the use of SAS software, version 8.2 (SAS Institute), and Stata software, version 11.0 (StataCorp). The data cutoff point was April 30, 2013.

RESULTS

PATIENTS

A total of 402 patients were enrolled; 399 entered the common induction and mobilization phase, and 273 remained eligible for random assignment to consolidation therapy with high-dose melphalan or MPR. At the end of consolidation therapy, 251 patients were also eligible for the randomized comparison between maintenance therapy and no maintenance therapy (Fig. 1). Baseline demographic and disease characteristics were well balanced among the treatment groups (Table S2 in the Supplementary Appendix). At the data cutoff point, 237 patients had disease progression or had died, 45 patients (23%) were still receiving lenalidomide maintenance therapy, and 24 patients (11%) were not receiving maintenance therapy. The median duration of follow-up from the time of enrollment was 51.2 months (range, 1 to 66).

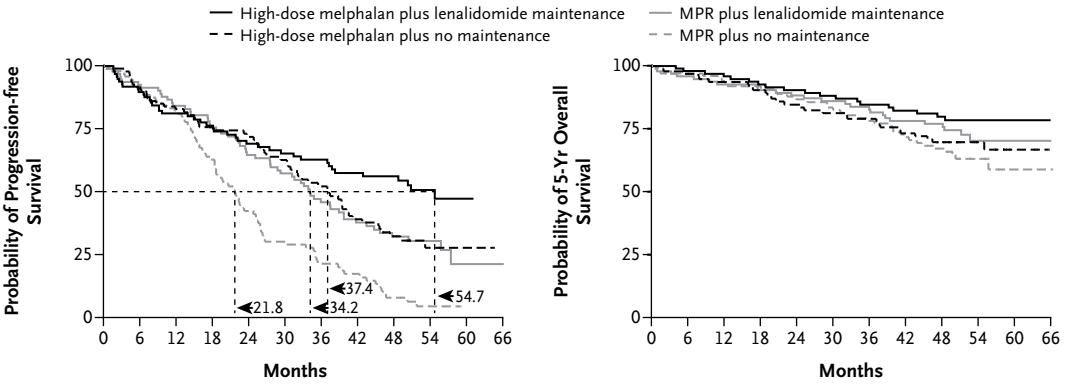
EFFICACY

In the total enrolled population (402 patients), the median progression-free survival from the time of diagnosis was 54.7 months among patients who received high-dose melphalan plus lenalidomide maintenance therapy, 37.4 months among patients who received high-dose melphalan without maintenance therapy, 34.2 months among patients who received MPR plus lenalidomide maintenance therapy, and 21.8 months among patients who received MPR without maintenance therapy (Fig. 2A). The 5-year overall survival rate was 78.4% among patients who received high-dose melphalan plus lenalidomide maintenance therapy, 66.6% among patients who received high-dose melphalan without maintenance therapy, 70.2% among patients who received MPR plus lenalidomide maintenance therapy, and 58.7% among patients who received MPR without maintenance therapy (Fig. 2A).

At the end of the induction and mobilization phase, the random assignment to high-dose melphalan or MPR was disclosed for the 273 patients who were eligible for consolidation therapy. The median progression-free survival was significantly longer among patients who received high-dose melphalan (43.0 months) than among patients who received MPR (22.4 months; hazard ratio for progression or death, 0.44; 95% confidence interval [CI], 0.32 to 0.61; $P<0.001$) (Fig. 2B). High-dose melphalan, as compared with MPR, was also associated with improvement in the 4-year overall survival rate (81.6% vs. 65.3%; hazard ratio for death, 0.55; 95% CI, 0.32 to 0.93; $P=0.02$) (Fig. 2B). The progression-free survival benefit associated with high-dose melphalan was consistent across all patient subgroups (Fig. S2 in the Supplementary Appendix).

Among the 251 patients who were eligible to be included in the second randomized comparison (between lenalidomide maintenance therapy and no maintenance therapy), median progression-free survival was significantly longer with lenalidomide maintenance therapy than with no maintenance therapy (41.9 months vs. 21.6 months;

A From Time of Diagnosis

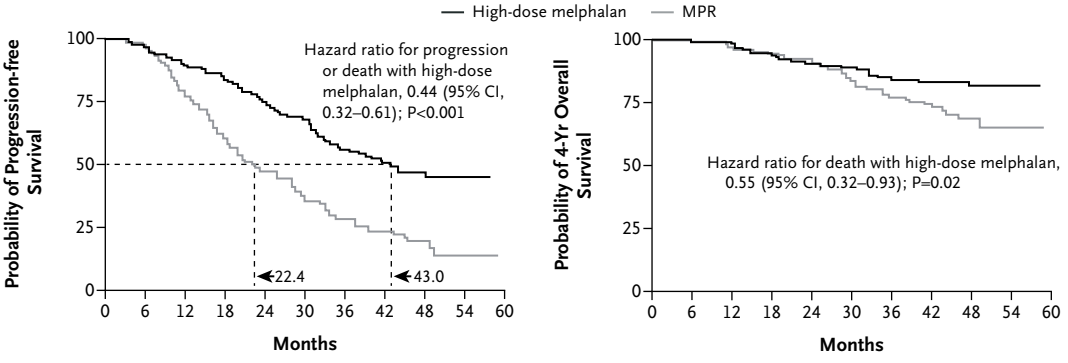


No. at Risk

High-dose melphalan plus lenalidomide maintenance	100	88	73	64	57	53	49	43	40	19	1
High-dose melphalan plus no maintenance	100	87	74	60	56	49	41	31	21	9	2
MPR plus lenalidomide maintenance	98	84	71	63	54	48	36	28	24	10	2
MPR plus no maintenance	104	87	77	55	36	26	18	14	7	2	0

High-dose melphalan plus lenalidomide maintenance	100	97	92	84	79	76	71	68	61	31	3
High-dose melphalan plus no maintenance	100	93	87	79	74	71	69	62	52	26	4
MPR plus lenalidomide maintenance	98	91	84	82	80	77	73	67	63	23	7
MPR plus no maintenance	104	96	93	87	81	77	72	65	56	23	3

B From Start of Consolidation

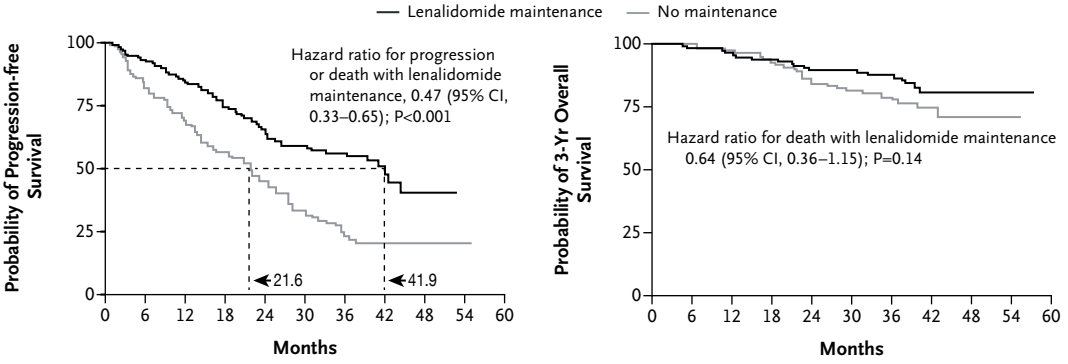


No. at Risk

High-dose melphalan	141	131	114	105	92	82	67	49	21	3	
MPR	132	128	98	76	57	41	32	25	7	1	

High-dose melphalan	141	136	129	121	115	111	105	88	42	7	
MPR	132	131	124	121	117	106	94	82	27	5	

C From Start of Maintenance



No. at Risk

Lenalidomide maintenance	126	112	100	86	73	62	51	15	2	0
No maintenance	125	96	78	64	51	37	20	9	2	1

Lenalidomide maintenance	126	120	115	110	103	100	83	32	7	2
No maintenance	125	117	114	109	99	94	71	25	6	2

Figure 2 (facing page). Kaplan–Meier Estimates of Progression-free Survival and Overall Survival.
Panel A shows progression-free survival and 5-year overall survival from the time of diagnosis among patients who received high-dose melphalan followed by lenalidomide maintenance therapy, those who received high-dose melphalan with no subsequent maintenance therapy, those who received MPR followed by lenalidomide maintenance therapy, and those who received MPR with no subsequent maintenance therapy. Panel B shows progression-free survival and 4-year overall survival from the start of consolidation therapy. Panel C shows progression-free survival and 3-year overall survival from the start of maintenance or no maintenance. The median progression-free survival is shown within the graph in the left side of each panel. CI denotes confidence interval.

hazard ratio for progression or death, 0.47; 95% CI, 0.33 to 0.65; P<0.001) (Fig. 2C). Lenalidomide maintenance therapy, as compared with no maintenance therapy, had no significant effect on the 3-year overall survival rate (88.0% vs. 79.2%; hazard ratio for death, 0.64; 95% CI, 0.36 to 1.15; P=0.14) (Fig. 2C). The beneficial effect of lenalidomide maintenance on progression-free survival was homogeneous in all subgroups except patients with stage III disease at the time of diagnosis (P=0.04 for the interaction between stage and treatment) (Fig. S2 in the Supplementary Appendix). Results of the subgroup analysis of overall survival are shown in Figure S3 in the Supplementary Appendix.

No significant differences in progression-free survival were detected between the maintenance and no-maintenance populations in the comparison of high-dose melphalan with MPR (P=0.99 for interaction) (Fig. S2 in the Supplementary Appendix), or between the high-dose melphalan and MPR subgroups in the comparison of lenalidomide maintenance therapy with no maintenance therapy (P=0.93 for interaction) (Fig. S2 in the Supplementary Appendix). Among patients with relapsed multiple myeloma, the 3-year overall survival rates from the time of relapse were similar across the four treatment groups (Fig. S4 in the Supplementary Appendix). In the MPR group, 98 of 156 patients (62.8%) received high-dose melphalan at relapse, as prespecified in the treatment protocol. Details of salvage treatment administered at the time of relapse are provided in Table S3 in the Supplementary Appendix.

The complete response rate improved from 15.7% after consolidation therapy to 35.7% after maintenance therapy in the high-dose melphalan group and from 20.0% after consolidation therapy to 33.8% after maintenance therapy in the MPR group (data not shown). Prognostic factors such as staging and cytogenetic features did not affect the quality of the response.

SAFETY

During the induction phase, the most frequent grade 3 or 4 adverse events were neutropenia (in 8.5% of the patients), anemia (in 6.3%), infection (in 6.0%), and dermatologic events (in 4.8%); one death occurred as a result of arrhythmia. In total, 27 of 399 patients (6.8%) discontinued treatment because of adverse events, and 56 (14.0%) discontinued treatment for other reasons (withdrawal of consent or the investigator's decision) (Table 1).

During consolidation therapy, hematologic adverse events occurred more frequently in patients who received high-dose melphalan than in those who received MPR. These events were mainly grade 3 or 4 neutropenia (94.3% vs. 51.5%, P<0.001) and thrombocytopenia (93.6% vs. 8.3%, P<0.001) (Table 1). Other grade 3 or 4 adverse events that were more common in patients who received high-dose melphalan were gastrointestinal events (18.4% vs. 0%, P<0.001), infections (16.3% vs. 0.8%, P<0.001), and systemic events (12.8% vs. 1.5%, P<0.001).

During the maintenance phase, the most frequent grade 3 or 4 adverse events were neutropenia (in 23.3% of patients who received lenalidomide maintenance therapy vs. 0% of patients who received no maintenance therapy, P<0.001), infections (in 6.0% vs. 1.7%, P=0.09), and dermatologic events (in 4.3% vs. 0%, P=0.03) (Table 1). Reduced doses of lenalidomide were required in 14.7% of patients (Table S5 in the Supplementary Appendix); 5.2% of patients discontinued lenalidomide because of toxicity (Table S6 in the Supplementary Appendix).

Eleven patients (2.8%) had a second primary cancer: lung cancer in one patient during induction; prostate cancer in two patients and breast cancer in three patients during lenalidomide maintenance therapy; and one case each of myelodysplasia, lung cancer, bladder cancer, colon cancer, and biliary tract cancer after consolidation ther-

Table 1. Grade 3 and 4 Adverse Events Occurring in at Least 2% of the Safety Population.*

Event	Induction Phase	Consolidation Phase		Maintenance Phase	
	Lenalidomide–Dexamethasone (N=399)	High-Dose Melphalan (N=141)	MPR (N=132)	Lenalidomide Maintenance (N=116)	No Maintenance (N=115)
	number of patients (percent)				
Hematologic adverse events					
Neutropenia	34 (8.5)	133 (94.3)	68 (51.5)	27 (23.3)	0
Thrombocytopenia	12 (3.0)	132 (93.6)	11 (8.3)	5 (4.3)	0
Anemia	25 (6.3)	32 (22.7)	2 (1.5)	2 (1.7)	0
Nonhematologic adverse events					
Gastrointestinal event†	7 (1.8)	26 (18.4)	0	—	—
Infection‡	24 (6.0)	23 (16.3)	1 (0.8)	7 (6.0)	2 (1.7)
Systemic event§	10 (2.5)	18 (12.8)	2 (1.5)	—	—
Dermatologic event¶	19 (4.8)	—	—	5 (4.3)	0
Vascular event‖	8 (2.0)	1 (0.7)	2 (1.5)	2 (1.7)	0
Second primary cancer — no. (%)**	1 (0.3)	0	0	5 (4.3)	5 (4.3)
Discontinuation of therapy due to adverse event	16 (4.0)	1 (0.7)	4 (3.0)	6 (5.2)	0
Discontinuation of therapy for other reasons					
Withdrawal of consent	13 (3.3)	8 (5.7)	1 (0.8)	6 (5.2)	0
Investigator's decision	21 (5.3)	4 (2.8)	0	3 (2.6)	0

* In categories for which no data are shown, the incidence was less than 2%.
† Gastrointestinal events included mucositis, nausea, vomiting, diarrhea, and constipation.
‡ Infections included pneumonia, bronchitis, sepsis, herpes zoster, gastrointestinal tract infection, influenza, cytomegalovirus infection, febrile neutropenia, and *Clostridium difficile* infection.
§ Systemic events included fatigue and fever of unknown origin.
¶ Dermatologic events included rash.
‖ Vascular events included deep-vein thrombosis, phlebitis, and pulmonary thromboembolic events.
** Second primary cancers were lung, prostate, breast, bladder, colon, and biliary tract cancers and myelodysplasia.

apy in patients who were randomly assigned to no maintenance therapy.

DISCUSSION

In this randomized study involving patients with newly diagnosed multiple myeloma, the standard high-dose melphalan consolidation therapy followed by stem-cell transplantation, as compared with MPR, was associated with a significant reduction in the risk of progression or death (hazard ratio, 0.44) and prolonged overall survival (hazard ratio for death, 0.55). Maintenance treatment with lenalidomide, as compared with no maintenance, was associated with a significantly reduced risk of disease progression or death (hazard ratio, 0.47). The best treatment strategy (induction followed by high-dose melphalan and lenalidomide maintenance) was associated with a 5-year rate of progression-free survival from the time of diagnosis of approximately 48% and an overall survival rate of 78% among all patients. These results confirm a net clinical benefit of high-dose melphalan administration as consolidation treatment and provide support for the benefit of lenalidomide as continuous treatment.

Despite a similar complete response rate with the two consolidation regimens, high-dose melphalan improved progression-free survival. Unfortunately, the response was assessed with the use of standard laboratory tests, and minimal residual disease was not monitored with immunophenotypic or molecular techniques, which might have revealed more subtle differences in the response, as reported in similar studies.[25] The clinical benefit was seen consistently across

the various patient subgroups. High-dose melphalan, as compared with MPR, was also associated with significant improvement in overall survival.

Hematologic and nonhematologic adverse events were more frequent with high-dose melphalan than with MPR. However, toxic effects were manageable and did not affect the rate of early death or treatment discontinuation or patients' ability to proceed to the maintenance or no-maintenance phase. Although stem cells were obtained from all patients at diagnosis, stem-cell transplantation was performed in only 62.8% of patients in the MPR group at the time of relapse, in most cases because of a rapid worsening of their clinical condition or the patient's decision to decline transplantation. Thus, stem-cell transplantation is not always feasible at the time of relapse, and the option of delayed transplantation should be suggested with caution.

The clinical benefit associated with lenalidomide maintenance was independent of the consolidation regimen. Response rates improved during maintenance therapy in both the high-dose melphalan and MPR groups. As compared with no maintenance, low-dose lenalidomide maintenance delayed relapse by approximately 2 years. Previous studies have shown that lenalidomide maintenance prolonged the duration of remission by 17, 18, and 19 months,[16-18] but an overall survival benefit was observed in only one of the three studies.[17] In our study, lenalidomide maintenance, as compared with no maintenance, was associated with significantly prolonged progression-free survival; no significant improvement in overall survival was noted. A longer follow-up study is needed to better evaluate the benefit of a delayed clinical relapse and the risk of chemoresistance after maintenance therapy. The benefit of maintenance therapy was seen in most subgroups, but a prespecified subgroup comparison showed no benefit in patients with stage III disease (hazard ratio, 1.06; $P=0.04$ for interaction).

Maintenance treatment with lenalidomide, as compared with no maintenance, was associated with more frequent grade 3 or 4 adverse events — mainly neutropenia and infections. Although maintenance therapy is effective in prolonging the duration of remission, it should be administered carefully to avoid toxic effects that may reduce the patient's quality of life. The rate of second primary cancers was low, and no between-group differences were reported.

This study had some limitations. First, only 68% of the enrolled patients were eligible to undergo the first randomization; the main reasons for discontinuation during the induction phase were disease progression and the patient's decision to choose an alternative therapy because of a suboptimal response after induction. Second, we investigated only lenalidomide and did not include bortezomib in the treatment plan. Bortezomib-based induction and consolidation regimens in combination with alkylating or immunomodulatory agents have been associated with unprecedented rates of high-quality response and a positive effect on outcomes in patients, regardless of whether they are eligible for stem-cell transplantation.[8,12] Third, placebo was not administered in the group of patients who did not receive maintenance therapy, and a blind assessment of progression was not made. Finally, quality-of-life assessments were not performed.

Ongoing large collaborative studies (the European Myeloma Network 02 trial and the Intergroupe Francophone du Myélome/Dana–Farber Cancer Institute 2009 trial; ClinicalTrials.gov numbers NCT01208766, NCT01191060, and NCT01208662) are evaluating effective drug combinations that include a proteasome inhibitor versus autologous stem-cell transplantation, the benefit of early versus late transplantation, and the effects of varying the duration of maintenance therapy. Results of these trials may shed further light on this important clinical area.

In conclusion, we found that consolidation therapy with high-dose melphalan, as compared with MPR, improved progression-free and overall survival, although at a cost of increased toxicity. Our findings confirm that high-dose melphalan remains the more effective therapeutic option in patients with newly diagnosed multiple myeloma. We also found that maintenance therapy with lenalidomide, as compared with no maintenance therapy, significantly reduced the risk of disease progression.

Supported by Celgene.

Dr. Palumbo reports receiving fees for serving on advisory boards from Amgen, Array BioPharma, Bristol-Myers Squibb, Celgene, Genmab, Janssen-Cilag, Millennium, Onyx, and Sanofi-Aventis; consulting fees from Amgen, Bristol-Myers Squibb, Celgene, Genmab, Janssen-Cilag, Millennium, and Onyx; lecture fees from Amgen, Bristol-Myers Squibb, Celgene, Janssen-Cilag, Millennium, and Onyx; and grant support from Janssen-Cilag, Millennium, and Onyx. Dr. Cavallo reports receiving fees for serving on an advisory committee from Celgene and honoraria from Janssen-Cilag, Onyx, and Celgene. Dr. Gay reports receiving honoraria from Janssen-Cilag and

Celgene, and fees for serving on advisory committees from Sanofi-Aventis and Celgene. Dr. Di Raimondo reports receiving lecture fees from Celgene, Janssen-Cilag, and Novartis. Dr. Petrucci reports receiving honoraria from Janssen-Cilag, Celgene, Sanofi-Aventis, and Bristol-Myers Squibb. Dr. Caravita reports receiving grant support from Celgene. Dr. Offidani reports receiving honoraria from Celgene and Janssen-Cilag. Dr. Patriarca reports receiving honoraria from Celgene, Janssen, and Merck Sharp & Dohme. Dr. Musto reports receiving fees for serving on advisory boards from Janssen-Cilag and lecture fees from Celgene and Janssen-Cilag. Dr. Nagler reports serving on a scientific advisory board for Novartis, receiving honoraria, consulting fees, and grant support from BioLineRx, CureTech, Medison, Neopharm Israel, Novartis, and Sigma Tau, and being a principal investigator for clinical studies funded by Celgene, CureTech, Johnson & Johnson, Merck, Millennium, Novartis, Onyx, and Sigma Tau. Dr. Boccadoro reports receiving fees for serving on scientific advisory boards, consulting fees, and grant support from Janssen-Cilag and Celgene. Dr. Cavo reports receiving fees for serving on advisory boards from Celgene, Janssen-Cilag, Millennium, Bristol-Myers Squibb, and Novartis, and consulting and lecture fees from Celgene, Janssen-Cilag, and Novartis. No other potential conflict of interest relevant to this article was reported. Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Federica Leotta and Giorgio Schirripa, from the coordinating site in Turin, for their assistance with the study, and Sandralee Lewis of the Investigator Initiated Research Writing Group (part of the KnowledgePoint360 Group, an Ashfield company), for her assistance with the preparation of an earlier version of the manuscript.

APPENDIX

The authors' full names and academic degrees are as follows: Antonio Palumbo, M.D., Federica Cavallo, M.D., Francesca Gay, M.D., Francesco Di Raimondo, M.D., Dina Ben Yehuda, M.D., Maria Teresa Petrucci, M.D., Sara Pezzatti, M.D., Tommaso Caravita, M.D., Chiara Cerrato, M.D., Elena Ribakovsky, M.D., Mariella Genuardi, M.D., Anna Cafro, M.D., Magda Marcatti, M.D., Lucio Catalano, M.D., Massimo Offidani, M.D., Angelo Michele Carella, M.D., Elena Zamagni, M.D., Francesca Patriarca, M.D., Pellegrino Musto, M.D., Andrea Evangelista, M.S., Giovannino Ciccone, M.D., Paola Omedé, Ph.D., Claudia Crippa, M.D., Paolo Corradini, M.D., Arnon Nagler, M.D., Mario Boccadoro, M.D., and Michele Cavo, M.D.

The authors' affiliations are as follows: the Myeloma Unit, Division of Hematology, University of Turin (A.P., F.C., F.G., C. Cerrato, M.G., P.O., M.B.), and Unit of Clinical Epidemiology and Centro di Referimento per l'Epidemiologia–Piemonte, Azienda Ospedaliero Universitaria Città della Salute e della Scienza di Torino (A.E., G.C.), Turin, Division of Hematology, Ospedale Ferrarotto, Azienda Policlinico–Ospedale Vittorio Emanuele, University of Catania, Catania (F.D.R.), Hematology, Sapienza University of Rome (M.T.P.), and Cattedra di Ematologia, Ospedale S. Eugenio–University Tor Vergata (T.C.), Rome, Divisione di Ematologia, Ospedale S. Gerardo, Monza (S.P.), La Struttura Complessa di Ematologia, Dipartimento di Ematologia ed Oncologia, Azienda Ospedaliera Niguarda Ca' Granda (A.C.), Hematology and Bone Marrow Transplantation Unit, San Raffaele Scientific Institute (M.M.), and Division of Hematology and Bone Marrow Transplantation, IRCCS Istituto Nazionale dei Tumori–University of Milan (P.C.), Milan, Ematologia, Policlinico Federico II, Naples (L.C.), Clinica di Ematologia, Azienda Ospedaliera Universitaria Ospedali Riuniti di Ancona, Ancona (M.O.), Unità Operativa Complessa Ematologia 1, IRCCS Azienda Ospedaliera Universitaria San Martino–Istituto Nazionale per la Ricerca sul Cancro, Genoa (A.M.C.), Seràgnoli Institute of Hematology, Bologna University School of Medicine, Bologna (E.Z., M.C.), Clinica Ematologia, Dipartimento di Scienze Mediche Sperimentali e Cliniche, Azienda Ospedaliera–Universitaria di Udine, Udine (F.P.), Scientific Direction, IRCCS, Centro di Riferimento Oncologico della Basilicata, Rionero in Vulture (P.M.), and Struttura Complessa Ematologia e Dipartimento Oncologia Medica, Spedali Civili di Brescia, Brescia (C. Crippa) — all in Italy; and the Hematology Division, Hadassah University Hospital, Jerusalem (D.B.Y.), and the Hematology Institute, Chaim Sheba Medical Center, Tel Hashomer (E.R., A.N.) — both in Israel.

REFERENCES

1. Attal M, Harousseau JL, Stoppa AM, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. N Engl J Med 1996;335:91-7.
2. 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.
3. Palumbo A, Anderson K. Multiple myeloma. N Engl J Med 2011;364:1046-60.
4. Palumbo A, Cavallo F. Have drug combinations supplanted stem cell transplantation in myeloma? Blood 2012;120:4692-8.
5. Benson DM Jr, Panzner K, Hamadani M, et al. Effects of induction with novel agents versus conventional chemotherapy on mobilization and autologous stem cell transplant outcomes in multiple myeloma. Leuk Lymphoma 2010;51:243-51.
6. Reece D. Update on the initial therapy of multiple myeloma. Am Soc Clin Oncol Educ Book 2013;33:e307-e312.
7. Harousseau JL, Attal M, Avet-Loiseau H, et al. Bortezomib plus dexamethasone is superior to vincristine plus doxorubicin plus dexamethasone as induction treatment prior to autologous stem-cell transplantation in newly diagnosed multiple myeloma: results of the IFM 2005-01 phase III trial. J Clin Oncol 2010;28:4621-9.
8. Cavo M, Tacchetti P, Patriarca F, et al. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. Lancet 2010;376:2075-85.
9. Sonneveld P, Schmidt-Wolf IG, van der Holt B, et al. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/ GMMG-HD4 trial. J Clin Oncol 2012;30:2946-55. [Erratum, J Clin Oncol 2012;30:3564.]
10. Facon T, Mary JY, Hulin C, et al. Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomised trial. Lancet 2007;370:1209-18.
11. Palumbo A, Bringhen S, Caravita T, et al. Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial. Lancet 2006;367:825-31.
12. San Miguel JF, Schlag R, Khuageva NK, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med 2008;359:906-17.
13. Richardson PG, Weller E, Lonial S, et al. Lenalidomide, bortezomib, and dexamethasone combination therapy in pa-

tients with newly diagnosed multiple myeloma. Blood 2010;116:679-86.
14. Palumbo A, Bringhen S, Rossi D, et al. Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: a randomized controlled trial. J Clin Oncol 2010;28:5101-9.
15. Falco P, Cavallo F, Larocca A, et al. Lenalidomide-prednisone induction followed by lenalidomide-melphalan-prednisone consolidation and lenalidomide-prednisone maintenance in newly diagnosed elderly unfit myeloma patients. Leukemia 2013;27:695-701.
16. Attal M, Lauwers-Cances V, Marit G, et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. N Engl J Med 2012;366:1782-91.
17. McCarthy PL, Owzar K, Hofmeister CC, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. N Engl J Med 2012;366:1770-81.
18. Palumbo A, Hajek R, Delforge M, et al. Continuous lenalidomide treatment for newly diagnosed multiple myeloma. N Engl J Med 2012;366:1759-69. [Erratum, N Engl J Med 2012;367:285.]
19. Ludwig H, Durie BG, McCarthy P, et al. IMWG consensus on maintenance therapy in multiple myeloma. Blood 2012; 119:3003-15.
20. Greipp PR, San Miguel J, Durie BG, et al. International Staging System for multiple myeloma. J Clin Oncol 2005;23:3412-20.
21. Cavallo F, Bringhen S, Milone G, et al. Stem cell mobilization in patients with newly diagnosed multiple myeloma after lenalidomide induction therapy. Leukemia 2011;25:1627-31.
22. Larocca A, Cavallo F, Bringhen S, et al. Aspirin or enoxaparin thromboprophylaxis for patients with newly diagnosed multiple myeloma treated with lenalidomide. Blood 2012;119:933-9.
23. Durie BG, Harousseau JL, Miguel JS, et al. International Uniform Response Criteria for Multiple Myeloma. Leukemia 2006;20:1467-73. [Errata, Leukemia 2006; 20:2220, 2007;21:1134.]
24. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE), v3.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf).
25. Rocci A, Gambella M, Omedè P, et al. Minimal residual disease monitoring during maintenance in multiple myeloma patients. Blood 2013;122:3126 (http://www.bloodjournal.org/content/122/21/3126).