The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 6, 2017 VOL. 376 NO. 14

Lenalidomide, Bortezomib, and Dexamethasone with Transplantation for Myeloma

Michel Attal, M.D., Valerie Lauwers-Cances, M.D., Cyrille Hulin, M.D., Xavier Leleu, M.D., Denis Caillot, M.D., Martine Escoffre, M.D., Bertrand Arnulf, M.D., Margaret Macro, M.D., Karim Belhadj, M.D., Laurent Garderet, M.D., Murielle Roussel, M.D., Catherine Payen, M.D., Claire Mathiot, M.D., Jean P. Fermand, M.D., Nathalie Meuleman, M.D., Sandrine Rollet, M.S., Michelle E. Maglio, B.S., Andrea A. Zeytoonjian, B.S., Edie A. Weller, Ph.D., Nikhil Munshi, M.D., Kenneth C. Anderson, M.D., Paul G. Richardson, M.D., Thierry Facon, M.D., Hervé Avet-Loiseau, M.D., Jean-Luc Harousseau, M.D., and Philippe Moreau, M.D., for the IFM 2009 Study*

ABSTRACT

BACKGROUND

High-dose chemotherapy plus autologous stem-cell transplantation has been the standard treatment for newly diagnosed multiple myeloma in adults up to 65 years of age. However, promising data on the use of combination therapy with lenalidomide, bortezomib, and dexamethasone (RVD) in this population have raised questions about the role and timing of transplantation.

METHODS

We randomly assigned 700 patients with multiple myeloma to receive induction therapy with three cycles of RVD and then consolidation therapy with either five additional cycles of RVD (350 patients) or high-dose melphalan plus stem-cell transplantation followed by two additional cycles of RVD (350 patients). Patients in both groups received maintenance therapy with lenalidomide for 1 year. The primary end point was progression-free survival.

RESULTS

Median progression-free survival was significantly longer in the group that underwent transplantation than in the group that received RVD alone (50 months vs. 36 months; adjusted hazard ratio for disease progression or death, 0.65; P<0.001). This benefit was observed across all patient subgroups, including those stratified according to International Staging System stage and cytogenetic risk. The percentage of patients with a complete response was higher in the transplantation group than in the RVD-alone group (59% vs. 48%, P=0.03), as was the percentage of patients in whom minimal residual disease was not detected (79% vs. 65%, P<0.001). Overall survival at 4 years did not differ significantly between the transplantation group and the RVD-alone group (81% and 82%, respectively). The rate of grade 3 or 4 neutropenia was significantly higher in the transplantation group than in the RVD-alone group (92% vs. 47%), as were the rates of grade 3 or 4 gastrointestinal disorders (28% vs. 7%) and infections (20% vs. 9%). No significant between-group differences were observed in the rates of treatment-related deaths, second primary cancers, thromboembolic events, and peripheral neuropathy.

CONCLUSIONS

Among adults with multiple myeloma, RVD therapy plus transplantation was associated with significantly longer progression-free survival than RVD therapy alone, but overall survival did not differ significantly between the two approaches. (Supported by Celgene and others; IFM 2009 Study ClinicalTrials.gov number, NCT01191060.)

From the Institut Universitaire du Cancer de Toulouse-Oncopole (M.A., M.R., C.P., S.R., H.A.-L.) and Service d'Epidémiologie, Centre Hospitalier et Universitaire de Toulouse (V.L.-C.), Toulouse, Hôpital Haut-Lévêque, Bordeaux Pessac (C.H.), Centre Hospitalier et Universitaire la Miletrie, Poitiers (X.L.), Centre Hospitalier Le Bocage, Dijon (D.C.), Centre Hospitalier et Universitaire de Rennes, Rennes (M.E.), Hôpital St.-Louis (B.A., J.P.F.), Centre Hospitalier Universitaire, Hôpital St.-Antoine (L.G.), Institut Curie (C.M.), and Haute Autorité de Santé (J.-L.H.), Paris, Institut d'Hématologie de Basse Normandie, Centre Hospitalier et Universitaire de Caen, Caen (M.M.), Centre Hospitalier et Universitaire Henri Mondor, Creteil (K.B.), Hôpital Claude Huriez, Lille (T.F.), and Hôtel Dieu, Nantes (P.M.) — all in France; Institut Jules Bordet, Brussels (N. Meuleman); and Dana–Farber Cancer Institute, Boston (M.E.M., A.A.Z., E.A.W., N. Munshi, K.C.A., P.G.R.). Address reprint requests to Dr. Attal at the Institut Universitaire du Cancer de Toulouse-Oncopole, 1 Ave. Irène Joliot Curie, 31059 Toulouse, France, or at attal.michel@iuct-oncopole.fr.

*A complete list of investigators in the Intergroupe Francophone du Myélome (IFM) 2009 Study is provided in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2017;376:1311-20.
DOI: 10.1056/NEJMoa1611750

For the past 20 years, high-dose chemotherapy plus autologous stem-cell transplantation has been the standard treatment for newly diagnosed multiple myeloma in adults up to 65 years of age.[1-3] However, this treatment requires hospitalization and can be associated with substantial toxic effects.

Over the past decade, immunomodulatory drugs[4-14] and proteasome inhibitors[15-17] have been shown to have substantial activity in patients with multiple myeloma. The use of combination therapy with immunomodulatory drugs, proteasome inhibitors, and dexamethasone has yielded increased rates of complete response and improved outcomes, both among patients who are eligible for transplantation and among those who are not.[18-21] The observed benefits of these combination therapies have led investigators to propose their use in adults with newly diagnosed multiple myeloma and have raised questions about the role and timing of transplantation in the initial treatment of such patients.

To address these issues, we conducted a phase 3 trial to compare the efficacy and safety of combination therapy with lenalidomide, bortezomib, and dexamethasone (RVD) alone with the efficacy and safety of RVD plus autologous stem-cell transplantation for the treatment of newly diagnosed multiple myeloma in adults up to 65 years of age.

Methods

Criteria for Enrollment

Eligible patients were 65 years of age or younger and presented with symptomatic, measurable, newly diagnosed multiple myeloma. (The terms symptomatic and measurable are defined in the study protocol, available with the full text of this article at NEJM.org.) Additional eligibility criteria were serum levels of aspartate aminotransferase and alanine aminotransferase of no more than 2 times the upper limit of the normal range, a serum bilirubin level of no more than 35 μmol per liter (2 mg per deciliter), creatinine clearance of at least 50 ml per minute, an absolute neutrophil count of at least 1000 per cubic millimeter, a platelet count of more than 50,000 per cubic millimeter, and normal cardiac and pulmonary function. Main exclusion criteria were peripheral neuropathy of grade 2 or higher and a history of other cancer. Women of childbearing potential were eligible if they agreed to use contraception, produced evidence of a negative pregnancy test before enrollment, and agreed to undergo monthly pregnancy testing until 4 weeks after discontinuation of the study medication. The protocol was approved by the institutional ethics committee at the coordinating center (Purpan Hospital, Toulouse, France). All the patients provided written informed consent.

Trial Design and Treatment

This randomized, open-label, phase 3 trial was conducted at 69 centers in France, Belgium, and Switzerland. Patients were recruited from November 2010 through November 2012 and were randomly assigned, in a 1:1 ratio, to one of two treatment groups during the first cycle of induction therapy. Randomization was stratified according to International Staging System disease stage (stage I, II, or III, with higher stages indicating more severe disease) and cytogenetic risk profile (standard risk, high risk, or risk undetermined because of test failure; high risk was defined by the presence of a t[4;14] translocation, t[14;16] translocation, or 17p deletion, as determined by fluorescence in situ hybridization).

All the patients received induction therapy with three 21-day cycles of RVD, which consisted of lenalidomide (25 mg, administered orally on days 1 through 14), bortezomib (1.3 mg per square meter of body-surface area, administered intravenously on days 1, 4, 8, and 11), and dexamethasone (20 mg, administered orally on days 1, 2, 4, 5, 8, 9, 11, and 12). After the induction phase, all the patients underwent stem-cell mobilization with cyclophosphamide and granulocyte colony-stimulating factor. During the consolidation phase, the patients received either five cycles of RVD with a reduced daily dose of dexamethasone of 10 mg (RVD-alone group) or melphalan at a dose of 200 mg per square meter plus autologous stem-cell transplantation followed by two cycles of RVD with a reduced daily dose of dexamethasone of 10 mg (transplantation group). In both treatment groups, maintenance therapy with lenalidomide (10 mg per day for the first 3 months, with a possible dose increase to 15 mg thereafter, depending on side effects) was initiated within the first 3 weeks after the completion of consolidation therapy and was continued for 1 year or until the occurrence of disease progression or unacceptable adverse events or the withdrawal

of patient consent (whichever came first). For patients in the RVD-alone group, salvage transplantation was recommended at the time of disease progression. A list of permitted concomitant therapies is provided in the Supplementary Appendix, available at NEJM.org.

END POINTS

The primary end point was progression-free survival. Secondary end points included response rate, time to disease progression, overall survival, and adverse event rates. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Serious adverse events and interim efficacy analyses were reviewed by an independent data and safety monitoring committee.

TRIAL OVERSIGHT

The senior academic authors designed the trial and wrote the first draft of the manuscript. Investigators at Toulouse Hospital collected the data and performed the analyses in collaboration with the senior academic authors and an independent data and safety monitoring committee. All the authors vouch for the accuracy and completeness of the data and analyses and for the fidelity of the study to the trial protocol. Celgene and Janssen provided lenalidomide and bortezomib, respectively, and provided funding but had no role in the analysis or interpretation of the data. Editorial assistance in the preparation of this manuscript was provided by a member of the Investigator Initiated Research Writing Group (an initiative from Ashfield Healthcare Communications, UDG Healthcare) and was funded by Celgene.

ASSESSMENTS

Treatment response and disease progression were assessed according to the International Uniform Response Criteria for Multiple Myeloma (see the Supplementary Appendix).[22] Complete disappearance of monoclonal protein (M protein) on standard clinical serum and urine immunofixation was considered to indicate a complete response if a bone marrow evaluation was performed and to indicate a very good partial response if a bone marrow evaluation was not performed. Blood and urine samples were obtained and immunofixation was performed every 4 weeks from randomization until disease progression. Among all the patients, bone marrow samples were obtained at enrollment for cytogenetic evaluation; among the patients who had a complete or very good partial response, bone marrow samples that had been obtained after the consolidation and maintenance phases were tested for minimal residual disease by means of seven-color flow cytometry (which has a sensitivity level of 10^{-4}, indicating that it can detect 1 malignant plasma cell within 10,000 bone marrow cells).[20] Minimal residual disease was detected if at least 50 plasma cells were observed in the bone marrow. Patients who had disease progression were followed up every 3 months to determine survival status.

STATISTICAL ANALYSIS

Assuming a median progression-free survival of 30 months in the RVD-alone group and 39 months in the transplantation group, we estimated that 700 patients would need to be enrolled to provide the trial with at least 80% statistical power to detect a 9-month longer progression-free survival in the transplantation group than in the RVD-alone group, with the use of a two-sided log-rank test at an overall significance level of 0.05. The statistical power was adjusted for two interim analyses, which were performed after 33% and 69% of the estimated disease progression events had occurred. Critical values at interim analysis were determined with the use of Lan–DeMets error spending functions corresponding to O'Brien–Fleming stopping boundaries.

The second interim analysis was performed in June 2015. The results were submitted to the independent data and safety monitoring committee, who allowed the results to be presented publicly at that time because the difference in progression-free survival met the prespecified stopping criterion ($P<0.015$). Progression-free survival was defined as the time from randomization until either the first documentation of disease progression or death from any cause. Censoring rules for progression-free survival followed the Food and Drug Administration guidance on end points in cancer trials. Time to progression was defined as the time from randomization until either the first documentation of disease progression or death owing to myeloma. Overall survival was defined as the time from randomization until death from any cause. Duration of follow-up after randomization was estimated by means of the reverse Kaplan–Meier method.[23]

Table 1. Baseline Characteristics of the Patients Who Underwent Randomization.*

Characteristic	RVD-Alone Group (N=350)	Transplantation Group (N=350)
Country — no. (%)		
France	343 (98)	345 (99)
Belgium	6 (2)	5 (1)
Switzerland	1 (<1)	0
Age — yr		
Median	59	60
Range	29–66	30–66
Male sex — no. (%)	208 (59)	214 (61)
Type of myeloma — no. (%)		
IgG	209 (60)	223 (64)
IgA	71 (20)	73 (21)
Light chain	57 (16)	46 (13)
Other	13 (4)	8 (2)
International Staging System disease stage — no. (%)		
I	115 (33)	118 (34)
II	170 (49)	171 (49)
III	65 (19)	61 (17)
Serum β_2-microglobulin level — no. (%)		
<3.5 mg/liter	169 (48)	178 (51)
3.5–5.5 mg/liter	116 (33)	111 (32)
>5.5 mg/liter	65 (19)	61 (17)
Cytogenetic abnormalities — no./total no. of patients who could be evaluated†		
t(4;14) translocation	26/256	28/259
17p deletion	15/256	16/258
t(14;16) translocation	6/256	6/258
t(4;14) or t(14;16) translocation or 17p deletion	44/256	46/259

* RVD therapy consists of lenalidomide, bortezomib, and dexamethasone. Percentages may not total 100 because of rounding.

† Data were obtained by means of fluorescence in situ hybridization. Patients could have more than one abnormality. For technical reasons, 94 patients in the RVD-alone group and 91 patients in the transplantation group could not be evaluated. Also, for technical reasons or because of an insufficient number of plasma cells, 1 additional patient in the transplantation group could not be evaluated for the 17p deletion, and 1 for the t(14;16) translocation.

Time-to-event end points were analyzed by means of the Kaplan–Meier method, with the use of a two-sided stratified log-rank test to compare the treatment groups and a multivariate Cox proportional-hazards model adjusted for stratification factors to estimate adjusted hazard ratios and 95% confidence intervals. A competing-risk analysis was performed to assess the effect of censoring events on progression-free survival.

Analyses of progression-free survival in specific subgroups were prespecified in the statistical analysis plan and were performed with the use of Cox proportional-hazards models with terms for treatment group, subgroup, and the interaction between subgroup and treatment group. The interaction terms were evaluated for statistical significance. Response rates were compared between groups with the use of a chi-square test or Fisher's exact test. Incidence rates of second primary cancers were calculated as the ratio of the number of second primary cancers to the number of patient-years at risk and were compared between groups with the use of a binomial exact test. P values for secondary efficacy end points and subgroup analyses were separately adjusted for multiplicity testing with the use of the Holm procedure to control the family-wise error rate at 0.05. Analyses were prespecified in the statistical analysis plan and were performed according to the intention-to-treat principle, with the use of Stata software, version 14.0 (StataCorp); the data cutoff date was September 1, 2015 (set by the steering committee).

RESULTS

PATIENTS AND TREATMENTS

Of the 764 patients who were screened for eligibility, 57 did not meet the eligibility criteria. In addition, 7 of the patients who began the first cycle of RVD induction therapy did not undergo randomization (because of a decision by the patient or investigator [5 patients] or a severe adverse event [2 patients]). Thus, 700 patients underwent randomization; 350 were assigned to each treatment group. Baseline characteristics were well balanced between the two treatment groups (Table 1).

In the RVD-alone group, 331 patients (95%) entered the consolidation phase and 321 (92%) entered the maintenance phase. In the transplantation group, 323 patients (92%) underwent transplantation, 315 (90%) began to receive RVD therapy after transplantation, and 311 (89%) entered the maintenance phase.

RESPONSE RATES

The rate of complete response was 48% in the RVD-alone group versus 59% in the transplantation group (P=0.03). The rate of complete or very

Table 2. Response to Treatment.*

Outcome	RVD-Alone Group (N=350)	Transplantation Group (N=350)	Adjusted P Value†
Best response during the study — no. (%)			0.02
Complete response	169 (48)	205 (59)	
Very good partial response	101 (29)	102 (29)	
Partial response	70 (20)	37 (11)	
Stable disease	10 (3)	6 (2)	
Complete response — no. (%)	169 (48)	205 (59)	0.03
Complete response or very good partial response — no. (%)	270 (77)	307 (88)	0.001
Minimal residual disease not detected during the study — no./total no. with complete or very good partial response (%)‡	171/265 (65)	220/278 (79)	<0.001

* Responses were assessed according to the International Uniform Response Criteria for Multiple Myeloma. Percentages may not total 100 because of rounding.
† P values were adjusted for multiplicity with the use of the Holm procedure to control the family-wise error rate at 0.05.
‡ Minimal residual disease was detected by means of flow cytometry. As a result of decisions made by the patient or the investigator, 5 patients in the RVD-alone group and 29 patients in the transplantation group were not tested.

good partial response was 45% in the RVD-alone group versus 47% in the transplantation group after the induction phase (P=0.87), 69% versus 78% after the consolidation phase (P=0.03), and 76% versus 85% after the maintenance phase (P=0.009); the rate was 70% after transplantation. Minimal residual disease was not detected in 65% of the patients in the RVD-alone group versus 79% of the patients in the transplantation group (P<0.001) (Table 2).

PROGRESSION-FREE SURVIVAL, TIME TO PROGRESSION, AND OVERALL SURVIVAL

The median duration of follow-up after randomization was 44 months in the RVD-alone group and 43 months in the transplantation group. Disease progression or death occurred in 368 patients (211 in the RVD-alone group and 157 in the transplantation group). Data for 7.2% of the patients in the RVD-alone group and 9.8% of the patients in the transplantation group were censored because the patients received a new therapy or a therapy that was not specified in the protocol, had consent withdrawn, or were lost to follow-up (Table S1 in the Supplementary Appendix).

Median progression-free survival was 36 months in the RVD-alone group versus 50 months in the transplantation group (adjusted hazard ratio for disease progression or death, 0.65; 95% confidence interval [CI], 0.53 to 0.80; P<0.001) (Fig. 1A). A competing-risk analysis led to numerically identical results (Fig. S1 in the Supplementary Appendix). Age, sex, isotype of the monoclonal component, International Staging System disease stage, and cytogenetic risk profile did not significantly modify the progression-free survival benefit associated with transplantation (Fig. 2). Progression-free survival was longer among patients in whom minimal residual disease was not detected than among those in whom minimal residual disease was detected (adjusted hazard ratio for disease progression or death, 0.30; P<0.001) (Figs. S2A and S3 in the Supplementary Appendix).

The median time to progression was 36 months in the RVD-alone group versus 50 months in the transplantation group (adjusted hazard ratio for disease progression or death owing to myeloma, 0.62; P<0.001). Overall survival at 4 years did not differ significantly between the two groups; the rate was 82% in the RVD-alone group and 81% in the transplantation group (adjusted hazard ratio for death, 1.16; 95% CI, 0.80 to 1.68; P=0.87) (Fig. 1B). Median survival was not reached in either group. Overall survival was longer among patients in whom minimal residual disease was not detected than among those in whom minimal residual disease was detected (adjusted hazard ratio for death, 0.34; P<0.001) (Fig. S2B in the Supplementary Appendix).

SALVAGE THERAPY

In the RVD-alone group, disease progression was reported in 207 patients, and 172 symptomatic

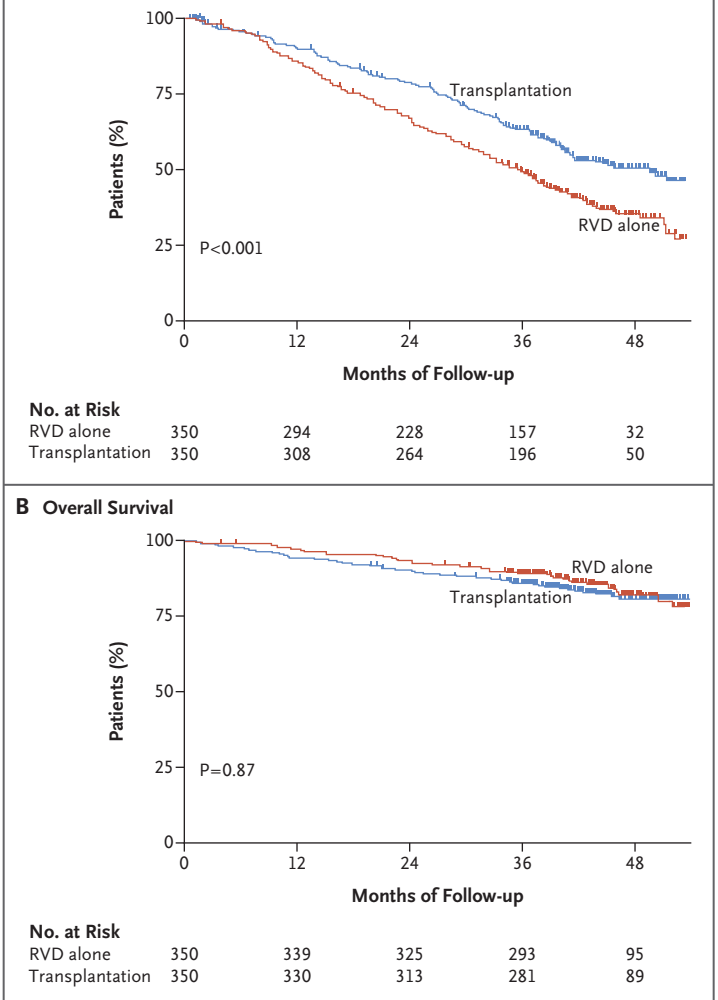

Figure 1. Kaplan–Meier Curves for Progression-free Survival and Overall Survival.

Panel A shows progression-free survival among patients who received RVD therapy (lenalidomide, bortezomib, and dexamethasone) alone and among those who received RVD therapy plus transplantation. Median progression-free survival was 50 months in the transplantation group and 36 months in the RVD-alone group (adjusted hazard ratio for disease progression or death, 0.65; 95% confidence interval [CI], 0.53 to 0.80; P<0.001). Panel B shows overall survival in the two treatment groups. Overall survival at 4 years did not differ significantly between the transplantation group and the RVD-alone group (adjusted hazard ratio for death, 1.16; 95% CI, 0.80 to 1.68; P=0.87).

patients received a second-line therapy. Second-line therapy was followed by salvage transplantation in 136 of the 172 patients (79%). Transplantation was not performed in the remaining 36 patients, mainly because of disease refractoriness. In the transplantation group, 149 patients had disease progression, and 123 symptomatic patients received a second-line therapy. Of the 123 patients who were treated for disease progression, 21 (17%) underwent a second transplantation at the time of progression. (Further details about second-line therapies are provided in Table S2 in the Supplementary Appendix.)

ADVERSE EVENTS

The most common grade 3 or 4 adverse events are listed in Table 3. In the RVD-alone group, treatment was discontinued in 32 patients (9%) because of adverse events, and two treatment-related deaths occurred. In the transplantation group, treatment was discontinued in 39 patients (11%) because of adverse events, and six treatment-related deaths occurred. Grade 3 or 4 adverse events that were significantly more common in the transplantation group than in the RVD-alone group were blood and lymphatic-system disorders (95% vs. 64%, P<0.001), gastrointestinal disorders (28% vs. 7%, P<0.001), and infections (20% vs. 9%, P<0.001).

SECOND PRIMARY CANCERS

The incidence of second primary cancers did not differ significantly between the two treatment groups (Table S3 in the Supplementary Appendix). The incidence of invasive second primary cancers was 1.1 cases per 100 patient-years in the RVD-alone group and 1.5 cases per 100 patient-years in the transplantation group (P=0.37). An updated analysis performed in September 2016 (Table S4 in the Supplementary Appendix) showed no significant between-treatment difference in the incidence of invasive second primary cancers (P=0.36). Five cases of acute myeloid leukemia occurred: 1 in the RVD-alone group, and 4 in the transplantation group (P=0.21).

DISCUSSION

Before the introduction of immunomodulatory drugs and proteasome inhibitors, several randomized trials showed that high-dose chemotherapy plus autologous stem-cell transplantation was superior to conventional chemotherapy for the treatment of multiple myeloma.[1,2] In the consolidation phase of our trial, we compared high-dose chemotherapy plus transplantation with RVD therapy, which consists of a combination of new agents, including lenalidomide and bortezo-

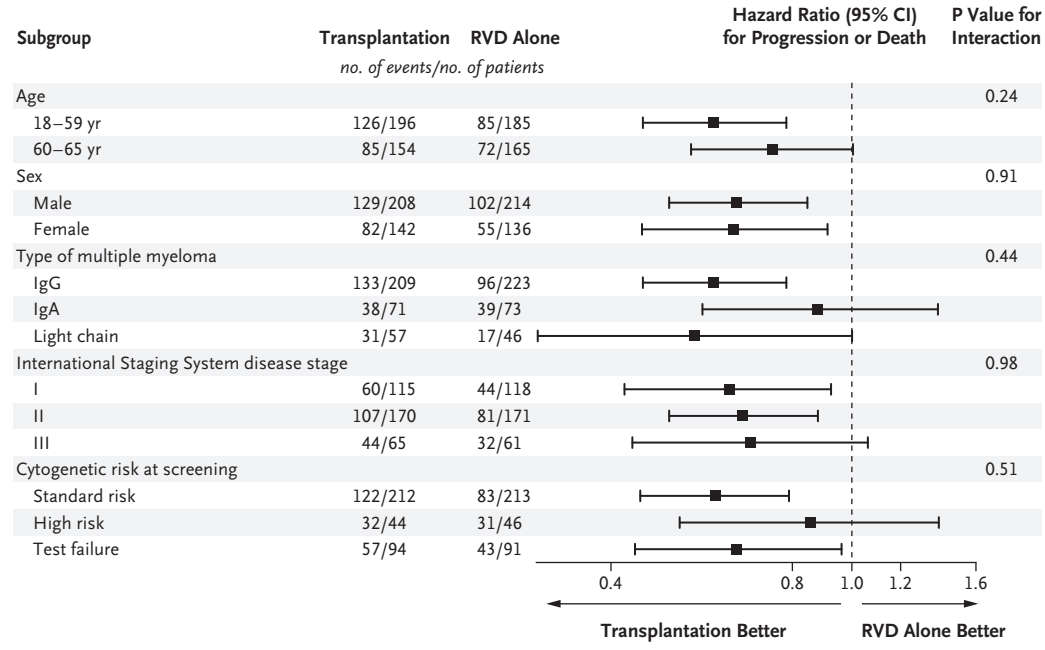

Figure 2. Subgroup Analyses of Progression-free Survival.

RVD therapy consists of lenalidomide, bortezomib, and dexamethasone. The P values shown have not been adjusted for multiple comparisons; P=1.00 after adjustment for multiple comparisons in each subgroup.

mib. We found that consolidation therapy with high-dose chemotherapy plus transplantation was associated with significantly longer progression-free survival (the primary end point) than RVD therapy alone in patients with newly diagnosed myeloma. Transplantation was also associated with a higher rate of complete response, a lower rate of minimal residual disease detection, and a longer median time to progression.

Overall survival was high and was similar in the two treatment groups. These results might be related to the use of RVD therapy in both treatment groups and to the high level of activity of the new agents that were used to treat relapses.[24] The similarity in overall survival in the two groups may also be related to the successful use of salvage transplantation. Several randomized trials that compared first-line transplantation with conventional chemotherapy, in which salvage transplantation was allowed, showed a progression-free survival benefit associated with first-line transplantation but no significant difference between treatments in overall survival.[3] Two recent studies in which transplantation was compared with an alkylating agent–based regimen plus lenalidomide followed by salvage transplantation showed an overall survival benefit associated with first-line transplantation.[25,26] However, all these nontransplantation regimens did not include proteasome inhibitors, have not been shown to lead to higher survival rates than those with melphalan–prednisone,[27] and resulted in poorer outcomes than those associated with transplantation. Data from our study suggest that delayed transplantation is feasible and is associated with no decrement in overall survival.

We found that the rate at which minimal residual disease was detected was lower among patients who received RVD plus transplantation than among those who received RVD alone. In addition, we observed longer overall survival among patients in whom minimal residual disease was not detected than among those in whom it was detected, regardless of treatment assignment. These findings confirm that the absence of minimal residual disease is an important treatment target in myeloma[28,29] and suggest that the use of high-dose chemotherapy plus transplantation after induction therapy with RVD specifically among patients in whom minimal residual

Table 3. Grade 3 and 4 Adverse Events That Occurred in At Least 2% of Patients.

Event	RVD-Alone Group (N=350)	Transplantation Group (N=350)
	number (percent)	
Any event	292 (83.4)	340 (97.1)
Blood and lymphatic system disorders	223 (63.7)	332 (94.9)
Neutropenia	166 (47.4)	322 (92.0)
Febrile neutropenia	12 (3.4)	52 (14.9)
Anemia	31 (8.9)	69 (19.7)
Thrombocytopenia	50 (14.3)	291 (83.1)
Gastrointestinal disorders	24 (6.9)	97 (27.7)
Nausea and vomiting	5 (1.4)	25 (7.1)
Stomatitis	0	59 (16.9)
Diarrhea	10 (2.9)	15 (4.3)
Hepatobiliary disorders	14 (4.0)	16 (4.6)
Cytolytic hepatitis	11 (3.1)	7 (2.0)
General disorders	22 (6.3)	30 (8.6)
Fatigue	7 (2.0)	6 (1.7)
Pyrexia	1 (0.3)	13 (3.7)
General deterioration of physical health	7 (2.0)	2 (0.6)
Infections	31 (8.9)	71 (20.3)
Respiratory tract infection	14 (4.0)	23 (6.6)
Sepsis	6 (1.7)	18 (5.1)
Nervous system disorders	48 (13.7)	59 (16.9)
Peripheral neuropathy	42 (12.0)	45 (12.9)
Grade 2 painful neuropathy	3 (0.9)	8 (2.3)
Skin disorders	18 (5.1)	11 (3.1)
Rash	7 (2.0)	4 (1.1)
Vascular disorders	11 (3.1)	14 (4.0)
Deep-vein thrombosis	5 (1.4)	10 (2.9)
Any thromboembolic event*	13 (3.7)	19 (5.4)

* Thromboembolic events include deep-vein thrombosis, pulmonary embolism, ischemic cardiopathy, and ischemic stroke.

disease is detected could be evaluated in future trials as one particular approach to tailoring therapy and further improving clinical benefit. In our trial, minimal residual disease was assessed by means of seven-color flow cytometry (sensitivity level, 10^{-4}).[20] It is possible that the more sensitive next-generation flow cytometry could have revealed more subtle differences and that patients in whom minimal residual disease was not detected in our trial may be considered to be patients in whom minimal residual disease is detected according to the new International Myeloma Working Group criteria.[30]

Maintenance treatment with lenalidomide after transplantation significantly improves outcomes among patients with newly diagnosed myeloma.[31,32] However, the duration of maintenance therapy remains a matter of debate. In our trial, maintenance therapy was administered for 1 year to limit toxic effects. In an ongoing, collaborative, parallel U.S. trial (the DETERMINATION study; ClinicalTrials.gov number, NCT01208662), which has a similar design to our trial, maintenance therapy with lenalidomide is being administered continuously until disease progression. A comparison of these two parallel trials will shed further light on this important question.

Grade 3 and 4 adverse events were more common with RVD plus transplantation than with RVD alone (97% vs. 83%). Five cases of acute myeloid leukemia occurred: four in the transplantation group, and one in the RVD-alone group. Although acute myeloid leukemia is part of the natural history of myeloma and its treatment, particularly in the context of melphalan use,[33] the patients in the transplantation group will require longer follow-up to accurately quantify this important risk.

In conclusion, we found that consolidation therapy with high-dose chemotherapy plus transplantation was associated with longer progression-free survival than RVD therapy alone. This benefit must be weighed against the increased risk of toxic effects associated with high-dose chemotherapy plus transplantation, especially since we found that later transplantation might be as effective as early transplantation in securing long-term survival. Our results suggest that the use of a combination therapy that incorporates newer proteasome inhibitors, next-generation immunomodulatory drugs, and potent monoclonal antibodies along with transplantation tailored according to minimal residual disease detection could further improve outcomes among adults up to 65 years of age who have multiple myeloma.[34-38]

Supported by grants from Celgene and Janssen and by funds from the French Ministry of Health Programme Hospitalier de Recherche Clinique and from the French National Research Agency (project ANR-11-PHUC-001-CAPTOR).

Dr. Hulin reports receiving honoraria from Bristol-Myers Squibb, Novartis, and Amgen; Dr. Belhadj, receiving consulting fees, travel support, and fees for serving on an advisory board from Celgene and travel support and fees for serving on advisory boards from Janssen, Novartis, and Amgen; Dr. Garderet, receiv-

ing fees for serving on advisory boards from Bristol-Myers Squibb, Takeda, and Amgen; Dr. Roussel, receiving fees for serving on advisory boards from Celgene and Janssen; Dr. Munshi, receiving consulting fees from Celgene, Merck, Takeda, Pfizer, Amgen, and Janssen, having ownership interest in OncoPep, and having a patent licensed to OncoPep for multipeptide vaccine (US 9,096,681 B2); Dr. Anderson, receiving fees for serving on advisory boards from Celgene, Millennium–Takeda, and Gilead Sciences and being scientific founder of Acetylon Pharmaceuticals, OncoPep, and C4 Therapeutics; Dr. Richardson, receiving research funding and fees for serving on advisory committees from Celgene and Millennium–Takeda and fees for serving on an advisory committee from Janssen; Dr. Facon, receiving consulting fees and travel support from Celgene, Janssen, and Sanofi and consulting fees from Amgen, Takeda, Bristol-Myers Squibb, and Novartis; and Dr. Moreau, receiving honoraria for serving on advisory boards from Celgene, Janssen, Novartis, Takeda, Amgen, and Bristol-Myers Squibb. 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 the members of the data and safety monitoring committee (Joan Blade, M.D., Ralph D'Agostino, Ph.D., Robert Kyle, M.D., Joseph Massaro, M.D., Jean Pearlstein, J.D., and Christian Straka, M.D.); representatives of Toulouse Hospital who were involved in data collection and analyses (Catherine Gentil, Laure Devlamynck, Pascale Olivier, Marie Elise Llau, and Marie Odile Petillon); and Sandralee Lewis, Ph.D., of the Investigator Initiated Research Writing Group (an initiative from Ashfield Healthcare Communications, UDG Healthcare) for editorial assistance in the preparation of an earlier version of the manuscript, funded by Celgene.

REFERENCES

1. 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.

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. Moreau P, Avet-Loiseau H, Harousseau JL, Attal M. Current trends in autologous stem-cell transplantation for myeloma in the era of novel therapies. J Clin Oncol 2011;29:1898-906.

4. 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.

5. Hulin C, Facon T, Rodon P, et al. Efficacy of melphalan and prednisone plus thalidomide in patients older than 75 years with newly diagnosed multiple myeloma: IFM 01/01 trial. J Clin Oncol 2009;27:3664-70.

6. 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.

7. Waage A, Gimsing P, Fayers P, et al. Melphalan and prednisone plus thalidomide or placebo in elderly patients with multiple myeloma. Blood 2010;116:1405-12.

8. Wijermans P, Schaafsma M, Termorshuizen F, et al. Phase III study of the value of thalidomide added to melphalan plus prednisone in elderly patients with newly diagnosed multiple myeloma: the HOVON 49 Study. J Clin Oncol 2010;28: 3160-6.

9. Beksac M, Haznedar R, Firatli-Tuglular T, et al. Addition of thalidomide to oral melphalan/prednisone in patients with multiple myeloma not eligible for transplantation: results of a randomized trial from the Turkish Myeloma Study Group. Eur J Haematol 2011;86:16-22.

10. Dimopoulos MA, Chen C, Spencer A, et al. Long-term follow-up on overall survival from the MM-009 and MM-010 phase III trials of lenalidomide plus dexamethasone in patients with relapsed or refractory multiple myeloma. Leukemia 2009; 23:2147-52.

11. Weber DM, Chen C, Niesvizky R, et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. N Engl J Med 2007;357:2133-42.

12. Dimopoulos M, Spencer A, Attal M, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. N Engl J Med 2007;357:2123-32.

13. Rajkumar SV, Jacobus S, Callander NS, et al. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. Lancet Oncol 2010;11:29-37.

14. Benboubker L, Dimopoulos MA, Dispenzieri A, et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. N Engl J Med 2014;371: 906-17.

15. 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.

16. Harousseau J-L, 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.

17. 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.

18. 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.

19. 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.

20. Roussel M, Lauwers-Cances V, Robillard N, et al. Front-line transplantation program with lenalidomide, bortezomib, and dexamethasone combination as induction and consolidation followed by lenalidomide maintenance in patients with multiple myeloma: a phase II study by the Intergroupe Francophone du Myélome. J Clin Oncol 2014;32:2712-7.

21. Richardson PG, Weller E, Lonial S, et al. Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma. Blood 2010;116:679-86.

22. Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. Leukemia 2006;20:1467-73.

23. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Control Clin Trials 1996;17:343-6.

24. Laubach JP, Voorhees PM, Hassoun H, Jakubowiak A, Lonial S, Richardson PG. Current strategies for treatment of relapsed/ refractory multiple myeloma. Expert Rev Hematol 2014;7:97-111.

25. Palumbo A, Cavallo F, Gay F, et al. Autologous transplantation and maintenance therapy in multiple myeloma. N Engl J Med 2014;371:895-905.

26. Gay F, Oliva S, Petrucci MT, et al. Chemotherapy plus lenalidomide versus autologous transplantation, followed by

lenalidomide plus prednisone versus lenalidomide maintenance, in patients with multiple myeloma: a randomised, multicentre, phase 3 trial. Lancet Oncol 2015; 16:1617-29.
27. Palumbo A, Hajek R, Delforge M, et al. Continuous lenalidomide treatment for newly diagnosed multiple myeloma. N Engl J Med 2012;366:1759-69.
28. Paiva B, Vidriales MB, Cerveró J, et al. Multiparameter flow cytometric remission is the most relevant prognostic factor for multiple myeloma patients who undergo autologous stem cell transplantation. Blood 2008;112:4017-23.
29. Rawstron AC, Child JA, de Tute RM, et al. Minimal residual disease assessed by multiparameter flow cytometry in multiple myeloma: impact on outcome in the Medical Research Council Myeloma IX Study. J Clin Oncol 2013;31:2540-7.
30. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol 2016;17(8): e328-e346.
31. 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.
32. McCarthy PL, Owzar K, Hofmeister CC, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. N Engl J Med 2012;366:1770-81.
33. Dong C, Hemminki K. Second primary neoplasms among 53 159 haematolymphoproliferative malignancy patients in Sweden, 1958-1996: a search for common mechanisms. Br J Cancer 2001;85:997-1005.
34. Stewart AK, Rajkumar SV, Dimopoulos MA, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. N Engl J Med 2015;372:142-52.
35. Moreau P, Masszi T, Grzasko N, et al. Oral ixazomib, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med 2016;374:1621-34.
36. Lokhorst HM, Plesner T, Laubach JP, et al. Targeting CD38 with daratumumab monotherapy in multiple myeloma. N Engl J Med 2015;373:1207-19.
37. Lonial S, Weiss BM, Usmani SZ, et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial. Lancet 2016;387:1551-60.
38. Lonial S, Dimopoulos M, Palumbo A, et al. Elotuzumab therapy for relapsed or refractory multiple myeloma. N Engl J Med 2015;373:621-31.