High-Dose Chemotherapy with Hematopoietic Stem-Cell Rescue for Multiple Myeloma

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ABSTRACT

BACKGROUND

High-dose therapy with supporting autologous stem-cell transplantation remains a controversial treatment for cancer. In multiple myeloma, first-line regimens incorporating high-dose therapy yield higher remission rates than do conventional-dose treatments, but evidence that this translates into improved survival is limited.

METHODS

In this multicenter study, the Medical Research Council Myeloma VII Trial, we randomly assigned 407 patients with previously untreated multiple myeloma who were younger than 65 years of age to receive either standard conventional-dose combination chemotherapy or high-dose therapy and an autologous stem-cell transplant.

RESULTS

Among the 401 patients who could be evaluated, the rates of complete response were higher in the intensive-therapy group than in the standard-therapy group (44 percent vs. 8 percent, P<0.001). The rates of partial response were similar (42 percent and 40 percent, respectively; P=0.72), and the rates of minimal response were lower in the intensive-therapy group than in the standard-therapy group (3 percent vs. 18 percent, P<0.001). Intention-to-treat analysis showed a higher rate of overall survival (P=0.04 by the log-rank test) and progression-free survival (P<0.001) in the intensive-therapy group than in the standard-therapy group. As compared with standard therapy, intensive treatment increased median survival by almost 1 year (54.1 months [95 percent confidence interval, 44.9 to 65.2] vs. 42.3 months [95 percent confidence interval, 33.1 to 51.6]). There was a trend toward a greater survival benefit in the group of patients with a poor prognosis, as defined by a high $beta_2$-microglobulin level (more than 8 mg per liter).

CONCLUSIONS

High-dose therapy with autologous stem-cell rescue is an effective first-line treatment for patients with multiple myeloma who are younger than 65 years of age.

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I N THE CONTROVERSIAL FIELD OF HIGH-dose chemotherapy, multiple myeloma is one disease in which this approach may provide tangible benefits, but data from rigorous studies are limited. In randomized trials carried out by the Medical Research Council of the United Kingdom between 1964 and 1990, the most effective standard regimen of conventional-dose chemotherapy consisted of doxorubicin, carmustine, cyclophosphamide, and melphalan and resulted in a median survival of 32 months.[1,2] Other conventional-dose regimens resulted in improved response rates, but not enduring remissions.[3] Escalating the doses of melphalan to a level requiring autologous stem-cell rescue[4-8] resulted in even higher rates of remission, with a complete response in approximately 50 percent of patients. An approach involving conventional-dose chemotherapy followed by high-dose therapy offered the prospect of a better outcome, but the evidence of a survival benefit has been inconclusive in nonrandomized[9-11] and randomized[12,13] studies. To investigate this strategy further, we initiated a phase 3 trial in which patients received either a standard regimen of doxorubicin, carmustine, cyclophosphamide, and melphalan or a regimen consisting of infusional combination chemotherapy followed by high-dose melphalan with autologous stem-cell transplantation. Both regimens included interferon alfa as maintenance therapy.

METHODS

PATIENTS

The Medical Research Council Myeloma VII Trial (ISRCTN66518389) was conducted from October 1993 to October 2000. All patients were previously untreated, fulfilled the Medical Research Council criteria for myeloma requiring treatment,[1] were less than 65 years of age, and were suitable candidates for high-dose therapy. Written informed consent was obtained from all patients. Randomization was by telephone and used a minimization algorithm based on age (<55 years vs. ≥55 years), serum creatinine level (<1.7 mg per deciliter [150 μmol per liter] vs. ≥1.7 mg per deciliter), hemoglobin level (<9 vs. ≥9 g per deciliter) and, in the latter part of the trial, whether total-body irradiation was intended as part of the conditioning regimen for transplantation. The trial was approved by a multicenter research ethics committee and by local ethics committees.

TREATMENT

Standard Therapy

Standard therapy consisted of a short infusion of 30 mg of doxorubicin per square meter of body-surface area intravenously and 30 mg of carmustine per square meter intravenously on day 1 followed by 100 mg of cyclophosphamide per square meter per day orally and 6 mg of melphalan per square meter per day orally on days 22, 23, 24, and 25. The cycle was repeated every six weeks until the maximal response was attained. A minimum of 4 cycles was given, and the maximum was 12 cycles. There were per-protocol dose reductions in the case of renal dysfunction, but patients who had treatment delays owing to myelosuppression received 300 mg of cyclophosphamide per square meter intravenously each week plus 40 mg of prednisolone per square meter orally every other day for the first six weeks. The planned maintenance therapy was 3 million U of interferon alfa-2a (Roferon-A) subcutaneously three times per week.

Intensive Therapy

Intensive therapy consisted of a continuous infusion of 9 mg of doxorubicin per square meter per day and 0.4 mg of vincristine per day on days 1 through 4, 1 g of methylprednisolone per square meter per day intravenously or orally (maximum, 1.5 g) on days 1 through 5, and 500 mg of cyclophosphamide per day intravenously on days 1, 8, and 15. The cycle was repeated every 21 days until a maximal response was attained. A minimum of three cycles was given before stem cells were harvested. Patients with a serum creatinine level of more than 3.4 mg per deciliter (300 μmol per liter) did not receive cyclophosphamide; cyclophosphamide was omitted on day 8 or 15 (or both) in the event of undue myelosuppression. Peripheral-blood stem cells were typically mobilized by the administration of 2 to 4 g of cyclophosphamide per square meter intravenously with hydration and granulocyte colony-stimulating factor on days 5 through 12. High-dose melphalan was given at a dose of 200 mg per square meter followed by the reinfusion of peripheral-blood stem cells 24 hours later. A bone marrow autograft and total-body irradiation plus melphalan (140 mg per square meter) were permissible options. Methylprednisolone (1.5 g per day) was given intravenously for four days after the administration of high-dose melphalan. The dose of melphalan

was reduced according to the creatinine clearance. The planned maintenance therapy was 3 million U of interferon alfa-2a administered subcutaneously three times per week.

ASSESSMENT OF RESPONSE

The response to treatment was monitored by means of serum and urine protein studies carried out centrally at the University of Birmingham. In the intensive-therapy group, the studies were conducted every three weeks during the chemotherapy regimen and every three months thereafter. In the standard-therapy group, the studies were conducted every three months. Bone marrow aspirates and trephine specimens were obtained as needed to determine the response to induction therapy, and also at three months and yearly after the completion of high-dose therapy and at relapse in the intensive-therapy group, and at the time of the maximal response and at progression in the standard-therapy group. The response criteria of the European Group for Blood and Marrow Transplantation–International Bone Marrow Transplant Registry[14] were used. A complete response was defined by the absence of monoclonal immunoglobulin in serum (or light chains in urine) on immunofixation. Causes of death were recorded by the participating centers as attributable to myeloma, infection, a variety of other secondary causes, unrelated causes, or combinations of these if the cause of death was considered to be multifactorial.

STATISTICAL ANALYSIS

Assuming the survival rate at four years to be 60 percent in the standard-therapy group, the study required 710 patients to have 80 percent power to detect an absolute improvement in survival of 10 percent in the intensive-therapy group. The recruitment target was 750 patients. The steering committee agreed to stop the trial in October 2000 when there was a total of 407 patients, in view of declining enrollment.

The primary end points were overall survival and progression-free survival. Overall survival was calculated from the date of randomization to the date of death from any cause. Data on patients who were lost to follow-up or who were alive at the time of analysis were censored in the survival analysis on the last date they were known to be alive. Progression-free survival was calculated from the date of randomization to the date of progression or death. Patients recorded as having died from multiple my-eloma and for whom no prior date for progression was available were considered to have had progressive disease on the day of death. Data on patients who had not had progression were censored on the last date they were known to be alive and progression-free. Survival curves were constructed with the use of Kaplan–Meier estimates, and treatment groups were compared with the use of the log-rank test at a significance level of 5 percent. Cox proportional-hazards models were used to adjust survival analyses for minimization factors (age, serum creatinine level, and hemoglobin level) and to investigate the correlation of the beta$_2$-microglobulin level with survival (which was specified in the statistical-analysis plan before any data were analyzed). A cut-off date of October 20, 2001, was used for survival analysis. The maximal response was compared in the treatment groups with the use of chi-square tests. The proportions of deaths recorded as solely or partly attributable to myeloma and solely or partly attributable to infection are reported, with 95 percent confidence intervals. All analyses were two-sided and carried out on an intention-to-treat basis with the use of SAS software (SAS Institute).

We used published data to conduct a meta-analysis of trials comparing conventional therapy with high-dose therapy in patients with myeloma. The resulting Forrest plot yielded an estimate of the odds ratio of the combined treatment effect, with 95 percent confidence intervals, with use of a fixed-effects approach. Analyses were performed with Review Manager software (version 4.1).[15]

RESULTS

CHARACTERISTICS OF THE PATIENTS AND TREATMENTS

A total of 407 patients were enrolled from 83 centers in the United Kingdom and New Zealand over a seven-year period from 1993 to 2000. Six patients could not be included in any data summaries or analyses: five underwent randomization in error, and one patient withdrew consent (Fig. 1). A total of 200 patients were randomly assigned to receive standard therapy and 201 to receive intensive therapy. The characteristics of the patients are summarized in Table 1. The myeloma subtypes were as follows: IgG in 56 percent of patients, IgA in 22 percent, IgD in 2 percent, light chain in 13 percent, and nonsecretory in 4 percent; data on subtype were missing in 3 percent of cases. Figure 1 summarizes the treatment received. In the intensive-therapy

Figure 1. Summary of Treatment Received.
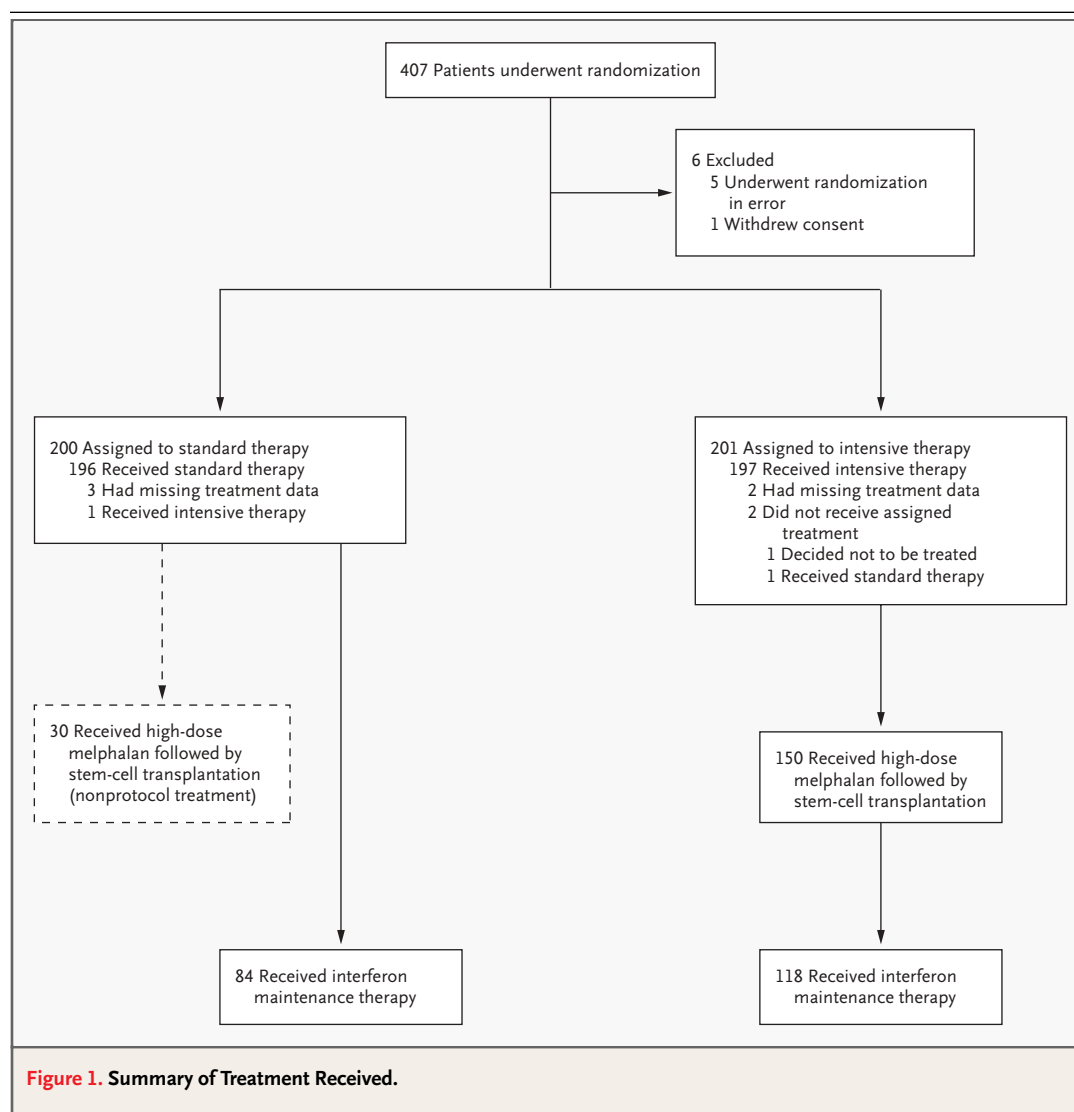
group, 197 patients received a median of five cycles (range, one to nine) of cyclophosphamide, vincristine, doxorubicin, and methylprednisolone. In the standard-therapy group, 146 patients received a median of 6 cycles (range, 1 to 13) of doxorubicin, carmustine, cyclophosphamide, and melphalan; 47 received doxorubicin, carmustine, cyclophosphamide, and melphalan as well as cyclophosphamide weekly for a median of 4 cycles (range, 1 to 12); and 3 received cyclophosphamide weekly alone.

In the intensive-therapy group, 50 of 201 patients (25 percent) did not receive high-dose melphalan, as a result of death, early disease progression (i.e., during induction chemotherapy), poor performance status, or low CD34 counts or by

choice, and thus did not receive a stem-cell transplant. Therapy with high-dose melphalan was usually supported by the reinfusion of peripheral-blood stem cells (138 patients [92 percent]); only 8 patients received bone marrow (5 percent), and 3 received both bone marrow and stem cells (2 percent; this information was unavailable for 1 patient). The dose of melphalan was reduced in 17 patients (11 percent), as a result of poor stem-cell harvests, renal failure, or poor performance status. Eight patients received total-body irradiation plus melphalan (140 mg per square meter). Two patients received a second autograft at relapse. Only 30 patients (15 percent) in the standard-therapy group went on to receive an autograft, and 4 (2 percent) an allograft,

as part of off-protocol therapy. In the standard-therapy group, 84 patients (42 percent) received interferon alfa-2a for at least a month, as compared with 118 patients (59 percent) in the intensive-therapy group. Among these patients, the drug was stopped because of intolerance or adverse events in 14 (17 percent) and 39 (33 percent), respectively, and because of disease progression in 43 (51 percent) and 33 (28 percent), respectively.
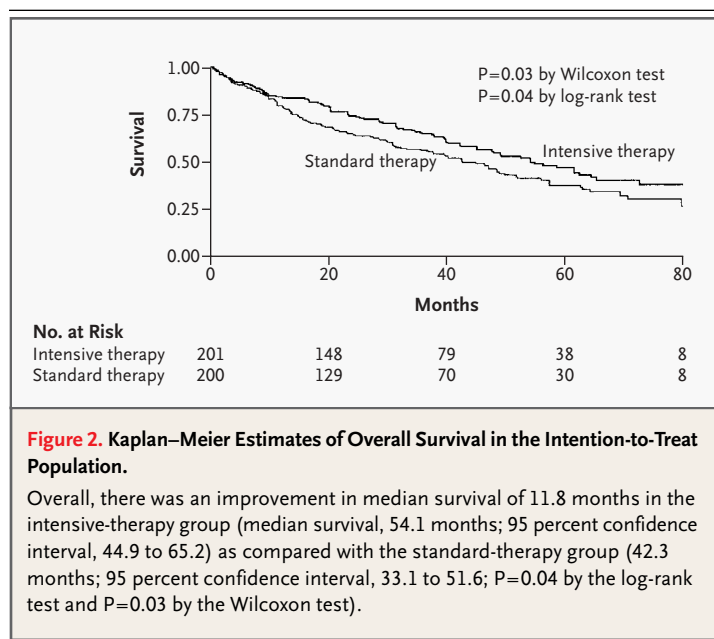
OVERALL SURVIVAL

As of October 20, 2001, 206 of the 401 patients (51 percent) had died: 112 patients in the standard-therapy group and 94 in the intensive-therapy group. The median duration of follow-up among survivors was 42 months (range, 9 to 96), with an overall median survival of 48.5 months (95 percent confidence interval, 42.2 to 56.3). The median survival was 54.1 months (95 percent confidence interval, 44.9 to 65.2) in the intensive-therapy group and 42.3 months (95 percent confidence interval, 33.1 to 51.6) in the standard-therapy group (P=0.04 by the log-rank test and P=0.03 by the Wilcoxon test) (Fig. 2). A Cox model that adjusted for minimization factors showed that survival rates were higher among patients with a creatinine level of less than 1.7 mg per deciliter than among those with a level of 1.7 mg per deciliter or higher and among patients with a hemoglobin level of 9 g per deciliter or higher than among those with a level of less than 9 g per deciliter. A significant interaction between treatment group and the beta$_2$-microglobulin level was seen (P=0.003 in the Cox model), indicating that the treatment effect varied depending on the level of beta$_2$-microglobulin. Stratified log-rank analysis according to the serum levels of beta$_2$-microglobulin — low (less than 4 mg per liter), intermediate (4 to 8 mg per liter), or high (more than 8 mg per liter) — defined in previous Medical Research Council studies[1] showed that within each stratum, the intensive-therapy group had a longer median survival than the standard-therapy group. This difference was greatest among those with base-line beta$_2$-microglobulin levels of more than 8 mg per liter. In these patients median survival was 41.9 months (95 percent confidence interval, 31.3 to 65.2) in the intensive-therapy group, as compared with 13.1 months (95 percent confidence interval, 9.2 to 23.9) in the standard-therapy group.

Table 1. Base-Line Characteristics of the Randomized Patients.

Characteristic	Standard Therapy (N=200)	Intensive Therapy (N=201)	Total (N=401)
Age — yr			
Median	56	55	55
Range	35–64	33–66	33–66
Sex — no. (%)			
Male	110 (55)	113 (56)	223 (56)
Female	90 (45)	88 (44)	178 (44)
Performance status — no. of patients (%)			
Normal activity	21 (10)	40 (20)	61 (15)
Symptoms, but ambulatory	123 (62)	114 (57)	237 (59)
In bed <50% of time	23 (12)	21 (10)	44 (11)
In bed ≥50% of time	22 (11)	20 (10)	42 (10)
100% bedridden	9 (4)	4 (2)	13 (3)
Data missing	2 (1)	2 (1)	4 (1)
Serum calcium — no. of patients (%)			
<2.6 mmol/liter (10.4 mg/dl)	139 (70)	133 (66)	272 (68)
≥2.6 mmol/liter	48 (24)	45 (22)	93 (23)
Data missing	13 (6)	23 (11)	36 (9)
Serum creatinine — no. of patients (%)			
<1.7 mg/dl	156 (78)	162 (81)	318 (79)
≥1.7 mg/dl	40 (20)	37 (18)	77 (19)
Data missing	4 (2)	2 (1)	6 (2)
Hemoglobin — no. of men (%)			
<11.5 g/dl	58 (53)	62 (55)	120 (54)
≥11.5 g/dl	52 (47)	51 (45)	103 (46)
Hemoglobin — no. of women (%)			
<9.5 g/dl	34 (38)	37 (42)	71 (40)
≥9.5 g/dl	56 (62)	51 (58)	107 (60)
Beta$_2$-microglobulin — no. of patients (%)			
<4 mg/liter	74 (37)	77 (38)	151 (38)
4–8 mg/liter	56 (28)	57 (28)	113 (28)
>8 mg/liter	43 (22)	52 (26)	95 (24)
Data missing	27 (14)	15 (7)	42 (10)

PROGRESSION-FREE SURVIVAL

As of October 20, 2001, 288 of the 395 patients who could be evaluated for disease progression (73 percent) had evidence of progression; 36 in the standard-therapy group and 71 in the intensive-therapy group remained progression-free. Overall, the median duration of progression-free survival was 25.1 months (95 percent confidence interval, 21.4 to 27.8). After a median follow-up of 31.5 months in the standard-therapy group and 40.0 months in the intensive-therapy group, 160 patients had evidence of progression in the standard-therapy group and 128 in the intensive-therapy group. The median duration of progression-free survival was 31.6 months (95 percent confidence interval, 27.4 to

Figure 2. Kaplan–Meier Estimates of Overall Survival in the Intention-to-Treat Population.

Overall, there was an improvement in median survival of 11.8 months in the intensive-therapy group (median survival, 54.1 months; 95 percent confidence interval, 44.9 to 65.2) as compared with the standard-therapy group (42.3 months; 95 percent confidence interval, 33.1 to 51.6; P=0.04 by the log-rank test and P=0.03 by the Wilcoxon test).

112 patients [62 percent; 95 percent confidence interval, 53 to 71] vs. 46 of 94 patients [49 percent; 95 percent confidence interval, 39 to 59]). Infection, as at least a contributory factor, was reported in 68 patients (33 percent) who died and was more frequent in the intensive-therapy group than in the standard-therapy group (35 patients [37 percent; 95 percent confidence interval, 27 to 47] vs. 33 patients [29 percent; 95 percent confidence interval, 21 to 38]). Six deaths occurred within 100 days after transplantation, five of which were due to sepsis. The rate of early death was not higher than expected in either group.

DISCUSSION

An approach involving high-dose chemotherapy with stem-cell rescue attempts to take advantage of the dose–response curve and often induces relatively high rates of tumor regression across a range of tumors, as compared with those achieved with conventional therapy. This has led to considerable enthusiasm for its use. It has increasingly been adopted as first-line treatment for multiple myeloma, despite the paucity of data from randomized trials providing convincing evidence of a survival benefit to support the routine use of this approach. Such studies are difficult and time-consuming to conduct, because of the technical complexity and, often, the strong beliefs about the effectiveness of one type of therapy or the other among clinicians and patients.

A systematic review of reports of trials comparing conventional with high-dose therapy[16] identified a number of randomized studies that clearly cannot be compared with our trial because of the timing of randomization (after response rather than at diagnosis),[17] the timing of transplantation (early vs. late),[18] use of higher-dose conventional therapy (so-called intermediate-dose melphalan),[19,20] and the number of transplantations (single vs. double).[21-23] Only two similar randomized studies were identified.[12,13] The Intergroupe Français du Myélome randomly assigned 200 patients to receive either conventional-dose combination chemotherapy or combination chemotherapy followed by melphalan (140 mg per square meter) with total-body irradiation.[12] Seventy-four patients in the intensive-therapy group underwent transplantation. The investigators reported a significant survival benefit with intensive therapy. In a recent update, the overall median duration of survival was 44 months in the

38.0) in the intensive-therapy group, as compared with 19.6 months (95 percent confidence interval, 16.2 to 21.8) in the standard-therapy group (P<0.001 by the log-rank or Wilcoxon test) (Fig. 3). Cox models showed that the serum creatinine level (P=0.001), hemoglobin level (P=0.07), and beta$_2$-microglobulin level (P=0.08) were significant prognostic factors for progression-free survival.

RESPONSE

The maximal response to randomized treatment is summarized in Table 2: the intensive-therapy group had a higher overall rate of response and a higher rate of complete remission than the standard-therapy group. Although no formal statistical tests were carried out, there was a trend toward improved survival in the intensive-therapy group as the extent of the response increased from minimal (25.6 months; 95 percent confidence interval, 7.0 to 31.3) to partial (39.8 months; 95 percent confidence interval, 33.8 to 61.4) to complete (88.6 months; lower 95 percent confidence limit, 61.4).

CAUSES OF DEATH

Of the 206 deaths, 183 (89 percent) were recorded as due to myeloma or related factors, including treatment. Multiple myeloma was cited as a causal factor in more patients in the standard-therapy group than in the intensive-therapy group (69 of

standard-therapy group and 56 months in the intensive-therapy group (Attal M: personal communication). A second study, by the Groupe Myélome Autogreffe, compared conventional-dose combination chemotherapy with infusional chemotherapy (with vincristine, doxorubicin, and dexamethasone) followed by melphalan at a dose of 200 mg per square meter or melphalan at a dose of 140 mg per square meter plus busulfan at a dose of 16 mg per square meter.[13] Of the 190 patients between the ages of 55 and 65 years who underwent randomization, 94 were assigned to the intensive-therapy group (25 percent of whom did not ultimately undergo transplantation). No significant survival benefit was seen with intensive treatment; the median overall duration of survival was 50.4 months in the conventional-chemotherapy group and 55.3 months in the intensive-therapy group. At the time of disease progression, patients in the conventional-chemotherapy group could cross over to receive high-dose therapy at their physicians' discretion.

We calculated the odds ratios and 99 percent confidence intervals for our study as well as for the Intergroupe Français du Myélome trial[12] and the Groupe Myélome Autogreffe trial[13] (Fig. 4). The two earlier studies together did not show a survival benefit. However, when our results were taken into account and the results of all three studies were combined, the estimated treatment effect was consistent with a significant survival benefit with intensive therapy, as compared with standard therapy (odds ratio, 0.70; 95 percent confidence interval, 0.53 to 0.93; P=0.01).

The most important finding in our trial was the increase in median survival of approximately one year among patients in the intensive-therapy group, as compared with those in the standard-therapy group. Per-protocol analyses showed that this difference may be a conservative estimate of benefit, because 17 percent of the patients in the standard-therapy group crossed over to high-dose therapy, usually after disease progression. Although myeloma and infection were commonly recorded as causes of death, any differences in the frequency of these causes between the two groups in a multicenter study of this nature should be treated with caution, since death was often multifactorial. There were only six deaths within 100 days after transplantation.

In the Medical Research Council trials, three subgroups corresponding to a good, an intermediate, and a poor prognosis have been delineated, on the
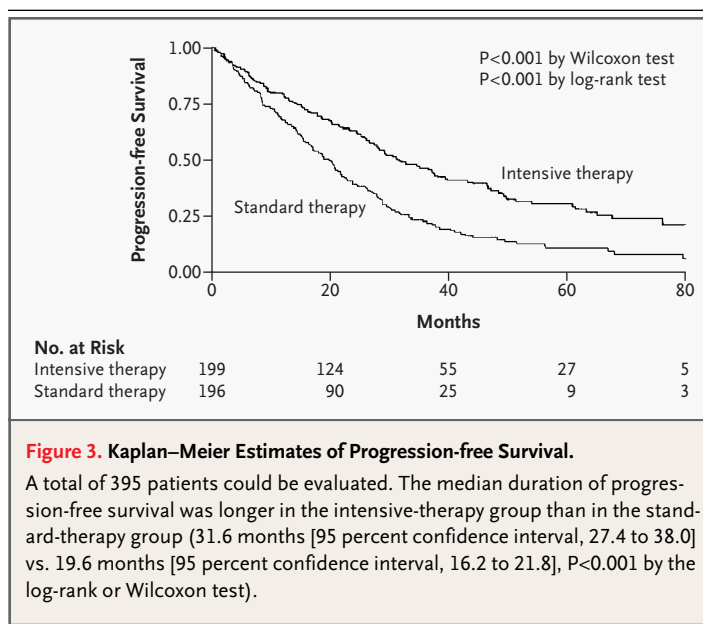

Figure 3. Kaplan–Meier Estimates of Progression-free Survival.
A total of 395 patients could be evaluated. The median duration of progression-free survival was longer in the intensive-therapy group than in the standard-therapy group (31.6 months [95 percent confidence interval, 27.4 to 38.0] vs. 19.6 months [95 percent confidence interval, 16.2 to 21.8], P<0.001 by the log-rank or Wilcoxon test).
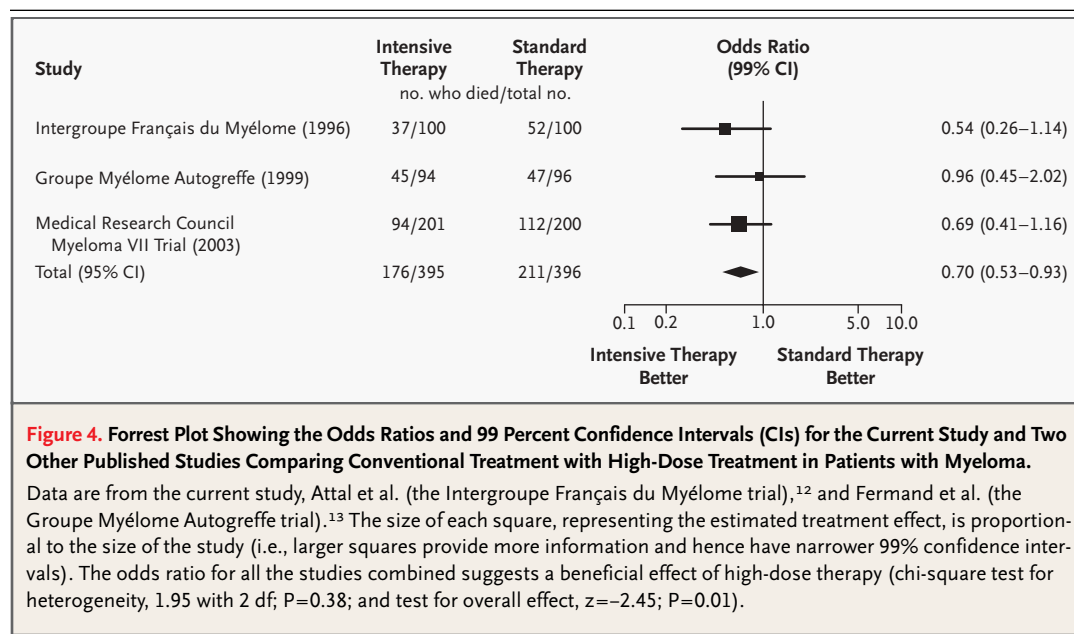
Table 2. Maximal Response to Treatment.*

Variable	Standard Therapy (N=200)	Intensive Therapy (N=201)	P Value†
	no. of patients (%)		
Complete response	17 (8)	89 (44)	<0.001
Partial response	81 (40)	85 (42)	0.72
Minimal response	35 (18)	7 (3)	<0.001
No change	30 (15)	4 (2)	
Progressive disease	19 (10)	3 (1)	
Unable to determine	10 (5)	4 (2)	
Early death‡	8 (4)	9 (4)	

* Response was defined according to the criteria of the European Group for Blood and Marrow Transplantation–International Bone Marrow Transplant Registry. Because of rounding, not all percentages total 100.
† P values were calculated with use of the chi-square test.
‡ Early death was defined as death within 60 days after randomization.

basis of serum beta$_2$-microglobulin levels (less than 4 mg per liter, 4 to 8 mg per liter, and more than 8 mg per liter, respectively).[1,24] In our study the proportions of patients in these groups were 38 percent, 28 percent, and 24 percent, respectively. A trend for patients in the group with a poor progno-

Figure 4. Forrest Plot Showing the Odds Ratios and 99 Percent Confidence Intervals (CIs) for the Current Study and Two Other Published Studies Comparing Conventional Treatment with High-Dose Treatment in Patients with Myeloma.

Data are from the current study, Attal et al. (the Intergroupe Français du Myélome trial),[12] and Fermand et al. (the Groupe Myélome Autogreffe trial).[13] The size of each square, representing the estimated treatment effect, is proportional to the size of the study (i.e., larger squares provide more information and hence have narrower 99% confidence intervals). The odds ratio for all the studies combined suggests a beneficial effect of high-dose therapy (chi-square test for heterogeneity, 1.95 with 2 df; P=0.38; and test for overall effect, z=−2.45; P=0.01).

sis to benefit most from intensive therapy was identified. Cytogenetic data were not generally available, but more recently, prognostic groups have been redefined by combining the serum beta$_2$-microglobulin level with 13q– status.[25-27]

We and others have previously shown a trend toward improved progression-free survival and overall survival among patients with undetectable myeloma protein in serum or urine (a complete response), as compared with those with a partial response.[27-29] In this study, we also identified a trend in the intensive-therapy group toward improved overall survival among patients who had a complete response. Further intensification of treatment through the use of multiple high-dose procedures to increase the rates of complete response remains under study.[21-23,27] Emerging biologic therapies may also offer a means of maintaining and enhancing such responses.

APPENDIX

The following institutions and clinicians participated in the study (members of the Medical Research Council Adult Leukaemia Working Party are indicated by asterisks): *New Zealand* — Christchurch Hospital: N. Patton, D. Hart, R. Spearings, S. Gibbons; Palmerston North Hospital, Palmerston North: B. Baker; *United Kingdom* — Airedale General Hospital, Keighley: A. Cuthbert; Altnagelvin Area Hospital, Londonderry: M. Ryan; Arrowe Park Hospital, Wirral: D. Galvani; Ashford Hospital, Ashington: A. Laurie; Belfast City Hospital, Belfast: C. Bharucha, Z. Desai; Birmingham Heartlands Hospital, Birmingham: C. Fegan, R. Johnson, D. Milligan*; Bradford Royal Infirmary, Bradford: L. Parapia, A. Williams; Bronglais General Hospital, Aberystwyth: H. Habboush; Cheltenham General Hospital, Cheltenham: R. Dalton, E. Blundell; Chesterfield and North Derbyshire Royal Hospital, Chesterfield: R. Collin, R. Stewart; Countess of Chester Hospital, Chester: V. Clough, E. Rhodes; City Hospital, Birmingham: D. Bareford; Derbyshire Royal Infirmary, Derby: A. McKernan, D. Mitchell; Dewsbury District Hospital, Dewsbury: M. Chapple; Diana Princess of Wales Hospital, Grimsby: K. Speed; Epsom General Hospital, Epsom: L. Jones; Freeman Hospital, Newcastle-upon-Tyne: P. Kesteven; George Eliot Hospital, Nuneaton: M. Narayanan; Gloucestershire Royal Hospital, Gloucester: S. Chown, J. Ropner; Good Hope Hospital, Sutton Coldfield: M. Hamilton, J. Tucker; Grantham and District Hospital, Grantham: V. Tringham; Harrogate District Hospital, Harrogate: A. Bynoe; Hillingdon Hospital, Uxbridge: R. Janmohamed; Horton General Hospital, Oxford: J. Durant*; Huddersfield Royal Infirmary, Huddersfield: C. Carter; John Radcliffe Infirmary, Oxford: P. Emerson; Kidderminster General Hospital, Kidderminster: M. Lewis; King's Mill Hospital, Sutton-in-Ashfield: E. Logan; Kingston General Hospital, Hull: M. Shields, C. Raper, R. Patmore; Leeds General Infirmary, Leeds: G. Smith, D. Norfolk; Leicester Royal Infirmary, Leicester: A. Hunter*, C. Chapman, J. Wood, R. Hutchinson, V. Mitchell; Lincoln County Hospital, Lincoln: M. Adelman; Middlesex Central Hospital, London: S. Davies; Nevill Hall Hospital, Abergavenny: H. Habboush; North Tyneside General Hospital, North Shields: H. Tinegate; Northern General Hospital, Sheffield: M. Brown; Northwick Park Hospital, Harrow: C. Reid; Nottingham University Hospital, Nottingham: G. Dolan; Pembury Hospital, Pembury: D. Gillett; Pilgrim Hospital, Boston: S. Sobolewski; Pinderfields General Hospital, Wakefield: P. Hillmen, M. Galvin; Pontefract Infirmary, Pontefract: R. Sibbald, J. Wright; Queen Elizabeth Hospital, Birmingham: J. Holmes; Queen Eliza-

beth Hospital, King's Lynn: P. Coates, A. Keidan; Queen's Hospital, Burton-upon-Trent: A. Smith; Rotherham General Hospital, Rotherham: H. Barker, P. Taylor; Royal Free Hospital, London: A. Mehta; Royal Liverpool Hospital, Liverpool: J. Cawley, P. Chu, R. Clark*; Royal South Hampshire Hospital, Southampton: A. Smith*; Russells Hall Hospital, Dudley: P. Harrison, S. Richardson; Sandwell District Hospital, West Bromwich: S. Handa, P. Stableforth; Scunthorpe General Hospital, Scunthorpe: S. Jalihal; Selly Oak Hospital, Birmingham: J. Murray; South Warwickshire Hospital, Warwick: P. Rose; Southampton General Hospital, Southampton: A. Provan; Southmead Hospital, Bristol: J. Hows, R. Slade; St. George's Hospital, London: J. Marsh, J. Parker-Williams; St. Helier Hospital, Carshalton: J. Mercieca; St. James's University Hospital, Leeds: B. McVerry, D. Barnard; St. John's Hospital at Howden, Livingston: M. Cook; Stafford District General Hospital, Stafford: P. Revell; Sunderland Royal Infirmary, Sunderland: D. Goff; Calderdale Royal Hospital, Halifax: A. Steed; Middlesex Hospital, London: R. Tobias; Ulster Hospital, Belfast: M. El-Agnaf; University Hospital of Wales, Cardiff: A. Burnett*, C. Poynton, J. Whitaker; Walton Hospital, Liverpool: W. Sadik, P. Stevenson; West Hill Hospital, Dartford: V. Andrews; Western General Hospital, Edinburgh: P. Ganly, P. Johnson, A. Parker, M. Mackie; Wolverhampton Hospital, Wolverhampton: A. Patel; Worcester Royal Infirmary, Worcester: A. Sawers; Wycombe General Hospital, High Wycombe: J. Pattinson; York District Hospital, York: L. Bond; Ysbyty Gwynedd, Bangor: H. Parry, J. Seale, H. Korn.

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