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Myeloma

Clinical outcomes with intensive therapy for patients with primary resistant multiple myeloma

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Summary:

Clinical outcomes were evaluated in 89 consecutive patients with multiple myeloma that had not responded to dexamethasone-based primary therapy, who received early intensive therapy supported by autologous stem cell transplantation. Results were compared with those of 45 comparable patients who refused or were unable to receive intensive treatment for socioeconomic reasons. Following high-dose therapy, the response rate was 69% including 16% with CR. Survival of 14 patients with CR (median >7.0 years) was significantly longer than those of 47 patients with PR (median 4.5 years) or of 28 patients who remained NR (median 2.2 years). CR occurred in 43% of patients with serum myeloma protein <1.5 gm/dl, in contrast to 7% of those with higher values, a finding similar to that observed previously for patients consolidated in PR. No prognostic factor was associated with PR and, in view of the high frequencies of PR or CR, all patients with primary resistant myeloma should be considered for early intensive therapy. The limited improvement of lifespan and disease-free survival for those in PR indicated the need for further treatment to achieve CR, the major surrogate marker for long survival.
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Early intensive therapy supported by autologous stem cells has been assessed in many groups of patients with multiple myeloma.[1–7] There is agreement that such treatment induces a higher frequency of CR and prolongs the median survival by approximately 1 year in comparison with those continued on standard therapies.[4,7] Certain prognostic factors, such as advanced disease, high B2M, deletion of chromosome 13 and treatment during later phases of disease have been associated with shorter survival.[8] Among those intensified during remission, we and others observed longer survival and relapse-free survival primarily among the one-third of patients converted to CR.[9–11] Prior rapid and marked reduction of myeloma with dexamethasone-based therapies were associated with even more frequent CR after intensive therapy, identifying prior tumor sensitivity as a predictive factor for CR.[11] Among patients whose disease had not responded to primary therapy, the role of intensive therapy has been less clear.

We analyzed outcomes of consecutive patients with primary resistant disease who received early intensive therapy with autologous stem cell transplantation. In comparison with a control group, survival was longer among those intensified and explained by the high frequencies of PR and CR. In view of acceptable toxicity, high frequency of remission and absence of any predictive factor that correlated with response, all patients with primary resistant disease are candidates for early intensive therapy.

Patients and methods

Patients

Between 1987 and 2002, 89 patients with primary resistant multiple myeloma received intensive therapy supported by autologous marrow or blood stem cells within the first year of treatment. Patient characteristics are summarized in Table 1. The myeloma was resistant both to initial treatment and any salvage chemotherapy program that was given within the first 9 months. The age was 60 years or less, all had good performance, and adequate cardiac, pulmonary and renal functions. Only patients with serum myeloma protein, with or without Bence Jones protein, were evaluated in order to distinguish the effects of NR, PR and CR with precision. All received intensive therapy after at least two courses of vincristine–doxorubicin by continuous infusion with pulse dexamethasone (VAD; 23 patients), pulse dexamethasone alone (43 patients) or in combination with melphalan (12 patients) or thalidomide (11 patients).[12–14] As clinical features, response rate and survival were similar among large series of patients who received each of these treatments, all patients were analyzed together.

Treatment

The median time between initial chemotherapy and intensive treatment was 6 months (range 2–12 months). Patients received one of four intensive programs prior to

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Table 1 Clinical features at diagnosis of patients who received intensive therapy for disease resistance and of control patients

	Transplanted	*Control*
No. of patients	89	45
Median age (years) (range)	52 (34–60)	53 (39–60)
Pretreatment features		
Tumor mass (%)		
High	28	18
Intermediate	43	36
Low	29	47
Hgb <10.5 g/dl (%)	62	33 ($P<0.05$)
Creatinine >2.0 mg/dl (%)	18	13
Serum B_2M (mg/l) (median and range)	3.7 (1.2–34.1)	3.6 (1.7–21.1)
LDH $>300\,\mu$/l (%)	4	7

autologous stem cell transplantation. A total of 12 patients received melphalan (140 mg/m^2) and TBI (850 cGy) from 1987 to 1991;[3] 36 received a combination of thiotepa (750 mg/m^2), busulfan (10 mg/kg) and cyclophosphamide (120 mg/kg) between 1991 and 1998;[15] 35 received melphalan alone 200 mg/m^2 from 1998 to 2002; and ^{166}holmium was added to the latter in six patients.[16] Within 48 h after completion of therapy, patients received either ABMT ($>1.0\times10^4$ granulocyte–macrophage colony-forming units/kg) (1987–1991) or autologous blood stem cells with $>2\times10^6$ CD34$^+$ mononuclear cells/kg (1992–2002). Autologous blood stem cells were collected in 79 patients, after cyclophosphamide priming in six patients or with neupogen alone in the remainder. As clinical features and outcomes were similar for patients who received different intensive treatments or sources of stem cells, all patients were combined in the analysis of transplant-supported therapy. There was no apparent effect of source of stem cells and time of study on frequencies of early death, PR, CR or survival.

Staging and response

Prior to initial therapy, standard criteria defined tumor mass as high, intermediate or low. High tumor mass required either Hb less than 8.5 g/dl or serum calcium higher than 11.5 mg/dl; intermediate tumor mass was defined by Hb between 8.5 and 10.5 g/dl or serum myeloma protein above 4.5 g/dl; low tumor mass required Hb above 10.5 g/dl and serum myeloma protein less than 4.5 g/dl. Partial response was defined as $>75\%$ reduction of serum myeloma protein production, $>95\%$ reduction of Bence–Jones protein when present and reduction of marrow plasmacytosis to less than 5%; CR required disappearance of serum myeloma protein by immunofixation on two consecutive studies for at least 3 months.[17] Patients in CR were followed without treatment, while those in PR were maintained on IFN 1.5–3.0 MU s.c. 3$\times$ weekly from the time of hematologic recovery.

Control patients

In all, 45 control patients were recognized with similar clinical features who were resistant to the same primary therapies and qualified for intensive therapy, but did not receive such treatment. Patients either refused therapy or were denied coverage by their insurance company. As in patients who received intensive therapy, control patients were 60 years old or less, presented with serum myeloma protein, received the same therapies during the same time period (1987–2002), were free of serious cardiac, pulmonary or renal dysfunction and would have received intensive treatment if possible. Control patients were treated earlier (median 7/93) in comparison with transplanted patients (median 10/98) and had less advanced disease features (Table 1).

Complete remission

Survival of patients who achieved CR after intensive therapy for primary resistant disease was compared with that of 50 patients who achieved CR after intensification of PR.[11] In total, 28 other patients achieved CR after diverse prior therapies with dexamethasone-based regimens between 1987 and 2002 (8% of those treated), of whom seven received subsequent consolidation therapy; the effect of CR on survival after standard therapy alone was assessed only in the remaining 21 patients.

Statistical analysis

χ^2 and log-rank tests were applied for comparison of baseline features of treatment and control groups. The Kaplan–Meier method was used to calculate survival time, and differences were compared by the log-rank test. Survival was measured from initial therapy for all patients and from the onset of CR for those who achieved that status; relapse-free survival for responsive patients was measured from the onset of remission to first sign of relapse. In an attempt to reduce bias, control patients were limited to those who lived at least 6 months after initial treatment by which time 51% of study patients had received intensive therapy.

Results

Partial or complete remission

After intensive therapy, PR or CR was induced in 61 patients (69%), including 14 patients with CR (16%). Treatment-related death occurred in five patients (6%), at a median 2 months after transplantation and 12 months after primary therapy. The frequency of remission was significantly higher than those observed among similar patients treated after 1 year with the same regimens and excluded from this study ($P<0.01$) (Figure 1). PR was confirmed by a median of 1.0 month and CR by a median of 4.6 months.

Survival and relapse-free survival

Deaths have occurred in 48% of all patients. The median survival was 27 months longer for transplanted patients than for control patients ($P<0.01$) (Figure 2, left panel) even though the latter showed more favorable prognostic features. The median survival was at least 7.0 years for

patients converted to CR, 4.5 years for those who achieved PR and 2.2 years for patients who remained NR ($P<0.01$) (Figure 2, right panel). Survival time of patients who remained NR was similar to that of control patients with primary resistant disease (median 2.0 years) ($P=0.8$). The median relapse-free survival of 47 patients with PR induced by intensive therapy was 2.9 years, similar to that of patients with PR after primary standard therapy.[13] Among 14 patients who achieved CR, the projected relapse-free survival was >7.0 years.

Frequency and impact of complete remission

The frequency of CR was assessed in a large number of patients of similar age, and treated from 1987 to 2002 with a dexamethasone-based regimen.

Applying the same criteria for CR (reproducible disappearance of serum myeloma protein by immunofixation), the frequency of CR increased from 8% for those who received only standard therapy, to 16% among those intensified for primary resistance and to 34% for those consolidated while in PR ($P<0.01$). Figure 3 shows similar survival from the onset of primary treatment (median 11.7 years) and from the onset of CR (median 10.3 years) for all patients who developed CR by the different pathways. An unrelated disease was the cause of death in four of 24

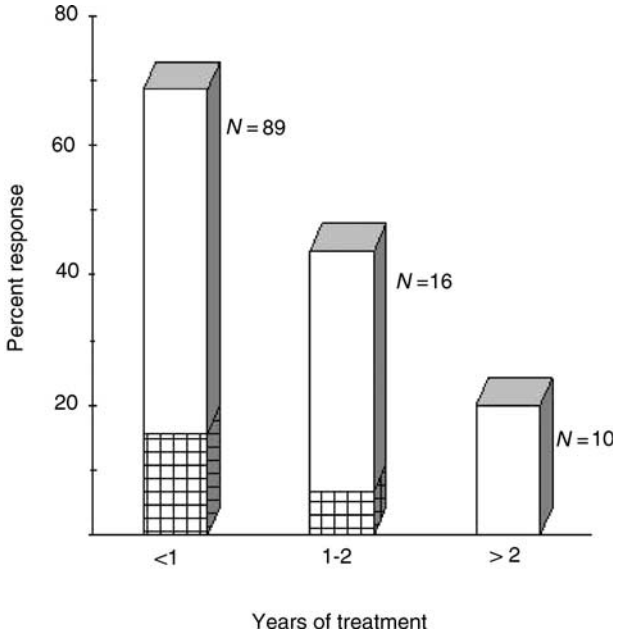

Figure 1 Progressively lower response rates with later intensive therapy for primary resistant myeloma. Response rates fell from 69% with treatment <1 year after primary therapy, to 44% for treatment between 1 and 2 years and to 20% for treatment >2 years later ($P<0.01$). Rates of CR also declined (stippled).

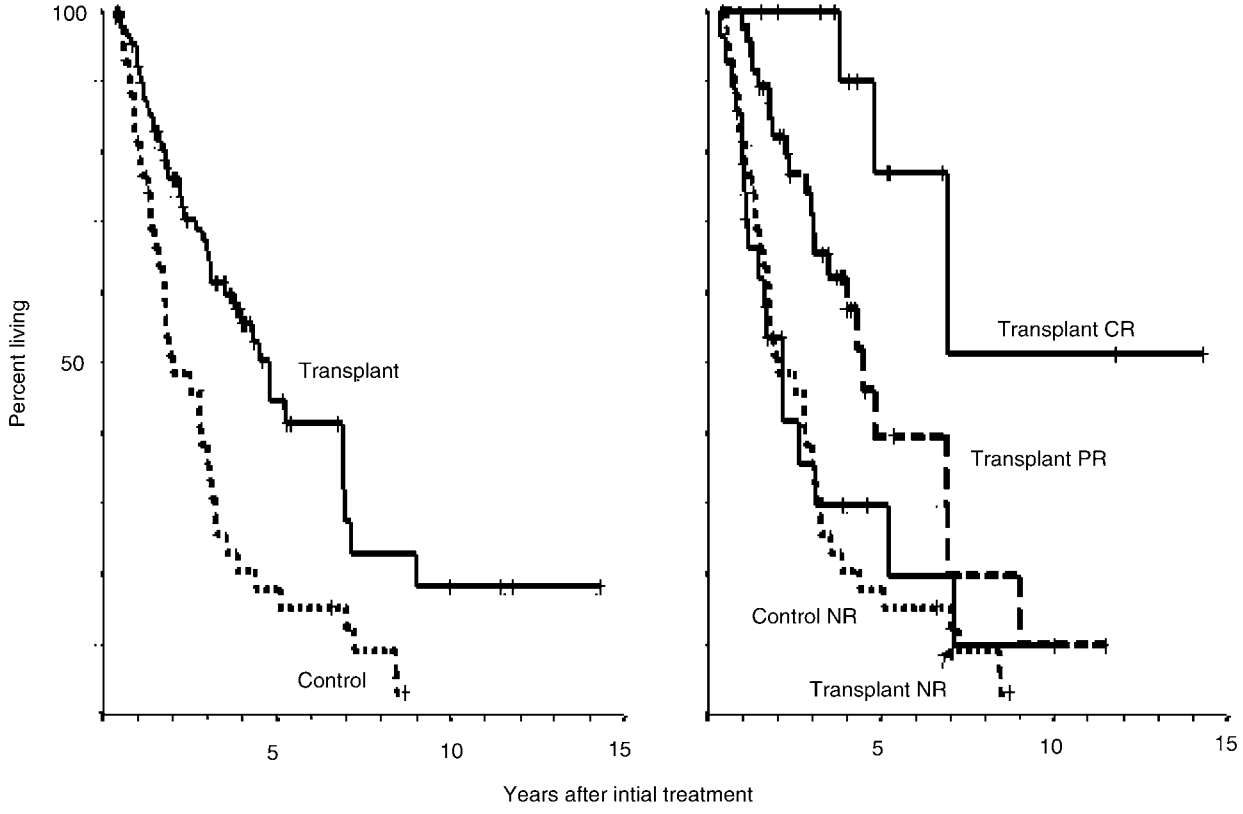

Figure 2 Left panel: Longer survival from primary treatment of 89 patients who received intensive therapy for resistant disease in comparison with 45 control patients continued on standard treatment ($P<0.01$). Right panel: Survival of 14 patients with disease converted from resistant status to CR, of 47 patients who achieved PR, of 28 patients with persistent NR and of 45 control patients with resistance to standard therapy ($P<0.01$).

patients who have died. The median relapse-free survival times were also similar at 8.7 years for all groups.

Prognostic factors

Multiple factors were assessed in order to identify those that might be associated with occurrence of PR or CR after intensive treatment. These included age, Hgb, creatinine, protein type, tumor mass, serum B2M and level of myeloma protein at diagnosis and prior to intensive treatment. Cytogenetics were not performed in sufficient patients for analysis. No factor was predictive of PR. However, CR was induced in 43% of patients with serum myeloma protein <1.5 gm/dl prior to transplantation, in comparison with 7% of those with higher levels ($P<0.01$).

Discussion

During the past 10 years, many studies have been conducted on the value of early intensive therapy supported by autologous stem cell transplantation for patients with multiple myeloma.[1–7] In two randomized studies, survival was longer for patients who received intensive therapy in comparison with control patients.[4,7] Benefit was attributed primarily to the higher frequency of CR in the 35% range with intensive therapy, in comparison with approximately 10% after standard therapies. We have described a 36% frequency of conversion of PR to CR that accounted for virtually all of the survival benefit among previously responsive patients.[11] Rapid and marked reductions of myeloma with primary therapy were followed by an even higher frequency of CR, identifying prior tumor sensitivity as a predictive factor.

The role of intensive therapy for patients with primary resistant disease has been less clear, perhaps because experiences with lymphoma indicated less benefit for patients with primary resistant disease.[18] We defined the efficacy of intensive therapy supported by autologous stem cell transplantation in a retrospective analysis of consecutive patients with disease that had not responded to VAD or similar programs with high-dose dexamethasone. Results were compared with those of control patients who qualified for transplantation in all respects, but either refused or were denied treatment for socioeconomic reasons. While control patients were treated 5 years earlier, they presented with less advanced disease, so that the countervailing effects on prognosis were probably balanced. Undetected selection factors may have excluded some patients from either group, perhaps biasing some outcomes, but such effects would have been small. The absence of consistent studies of cytogenetics was an important shortcoming.

Among patients with primary resistant disease intensified within 1 year, there was a high frequency of response of 69%, including 16% with CR, and with rapid onsets of remission. Later treatment was less effective perhaps because more resistant tumor cells had evolved with time, affirming the greater value of early intensive therapy for these patients. Thus, patients intensified for resistant disease lived approximately 2 years longer than controls; this difference was

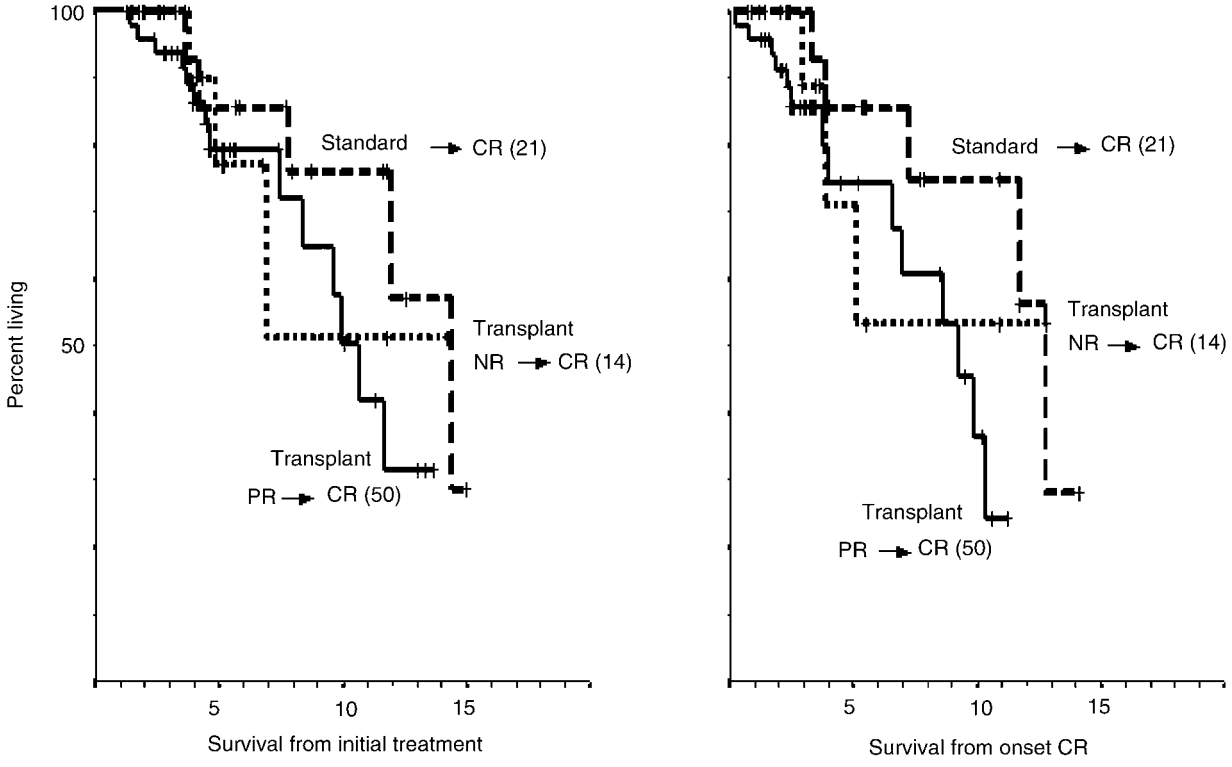

Figure 3 Left panel: Similar survival from primary therapy (median 11.7 years) of patients with increasing frequencies of CR after standard therapy, after intensive therapy of resistant disease or after intensive therapy of PR. Right panel: Similar survival (median 10.3 years) of same patients from the onset of CR.

attributed to the much longer lifespan of those few who achieved CR and to the doubling of survival for the majority who reached PR, in comparison with the short outcomes of those who remained NR. Consequently, longer lifespan was induced in twice as many patients with primary resistant myeloma (ie 69% achieved PR or CR) as those treated previously in PR (ie 34% converted from PR to CR).[11] In the absence of any dominant factor predictive of PR, all patients with primary resistant myeloma should be considered for early intensive therapy. Considering the acceptable tolerance of the procedure among older patients, there is no justification for the continued denial of medicare support for patients with primary resistant disease. Also, the higher risk of morbidity with time among patients with resistant disease lends urgency to the prompt review at diagnosis of the medical, social and financial eligibility for intensification. Primary chemotherapy that has been associated with rapid onsets of remission, such as one that includes high-dose dexamethasone, permits an earlier judgment on clinical response with facile collection of autologous blood stem cells despite residual marrow plasmacytosis.

Our study confirms previous findings on the value of intensive therapy for primary resistant myeloma.[19–21] Rajkumar *et al*[19] showed longer survival and progression-free survival for 12 patients with primary resistant disease in comparison with 63 other patients relapsing on or off therapy. Vesole *et al*[20] described a response rate of 65% and a median survival of 19 months for 56 patients with primary refractory disease affirming the feasibility of such therapy with better outcomes than those observed with standard salvage therapies. Singhal *et al* described results in 43 patients with primary resistance among whom the response rate was 70%; responding patients included 17 patients who achieved CR with a median event-free survival of approximately 4 years that was similar to those of 113 other patients who achieved CR after intensive therapy of initial CR or PR.[21] Our findings extend these observations by affirming that differences in survival depend primarily on the ultimate degree of response. Thus, the primary advantage with intensive therapy resulted from shifting a high percentage of patients from PR to CR, and from NR to PR or CR, changes that occurred in approximately one-half of patients treated within the first year. By implication, significant improvement of survival for patients on a clinical trial should be explained by higher partial and/or complete response rates and/or longer remission time.

While the frequency of CR differed among patients who received standard therapy, intensive therapy for resistant disease, or intensive therapy for PR, the median survival of approximately 11.7 years from initial therapy and 10.3 years from the onset of CR was similar for all groups. This observation conforms well with the report by Singhal on the long and similar disease-free survival of patients who achieved CR after intensive therapy despite their different pretransplant status.[21] Thus, the achievement of CR as a surrogate marker of long survival was more important than the pathway followed in reaching this goal. When one considers the long survival of patients in CR, the potential value of further intensive therapy for specific patients already in CR should be balanced against the expected lifespan from age and other disorders.

The median survival gain for patients who achieved PR was only 2 years longer than that of patients who remained NR, similar to the improved survival of newly diagnosed patients who achieved PR after standard therapies.[12,13] Thus, further measures should be considered for patients with primary refractory or partially responsive disease in order to increase the frequency of CR, which represents the major predictor of long survival.[4,10,11] These include experimental therapies that add ^{166}holmium DOTMP (a bone-seeking radioisotope) to high-dose melphalan or a sequence of intensive therapy with autologous cells followed by less intensive therapy with sibling-matched allogeneic cells to exploit a graft-versus-tumor effect.[16,22] Other programs to achieve CR, such as with velcade combinations, should also be explored.[23]

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