Intensive therapy for multiple myeloma in patients younger than 60 years. Long-term results focusing on the effect of the degree of response on survival and relapse pattern after transplantation

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Background and Objectives. From 1994 to 1997 we conducted a population-based, prospective study on intensive therapy in newly diagnosed symptomatic myeloma patients younger than 60 years, comparing their survival to that of a conventionally treated historic population. Long-term results are presented, including the impact of the degree of response on survival and relapse pattern after transplantation.

Design and Methods. The prospective population was formed of 397 patients and the historic population of 313 patients. Both populations were calculated to comprise more than 75% of the expected number of new cases.

Results. After a median follow-up of 7 years survival was longer in the prospective population than in the historic one (median 60 versus 39 months; p=0.0002). When comparing only patients eligible for intensive therapy the median survival was 63 versus 44 months (p<0.0001). Attaining a complete response was associated with prolonged event-free survival but not overall survival. The pattern of relapse after transplantation was heterogeneous but could be divided into four major groups; insidious, classical, plasmacytoma form and transformed disease. The median survival after relapse was 29 months. The relapse pattern and time to relapse predicted outcome. Patients relapsing with an insidious or classical form of disease with skeletal events only, or after a long lasting first response were likely to respond well to conventional salvage therapy. In contrast, relapse with multiple symptoms, transformed disease or a short duration of first response implied bad prognosis.

Interpretation and conclusions. The relapse pattern after autologous transplantation is heterogeneous and response to salvage therapy is variable. The degree of response and event-free survival after transplantation are not reliable surrogate markers for survival.

Key words: myeloma, transplantation, survival, response, relapse.

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Since the beginning of the 1990s there has been a considerable expansion in the use of intensive therapy with autologous stem cell transplantation for patients with multiple myeloma.[1] In 1994 the Nordic Myeloma Study Group started a study (NMSG #5/94) whose primary aim was to evaluate, in a population-based setting, the impact of intensive therapy on survival in patients younger than 60 years with newly diagnosed, symptomatic myeloma. The survival in this group was compared to that of historic controls, derived from previous Nordic population-based studies. Inclusion was stopped in December 1997. A first report, comprising the 348 patients who were registered until June 1997, has been published.[2] We here present the final results of the study of 397 registered patients with a median follow-up of 7 years. In this report we also analyze the pattern and management of relapse after transplantation and evaluate the effect on survival of both the relapse pattern and attaining complete response after transplantation.

Design and Methods

Fourteen centers in Denmark, Norway and Sweden, for a total catchment population of 15 million, were requested to register all newly diagnosed cases of symptomatic myeloma in patients younger than 60 years within their regions from March 1994 to December 1997. A total of 397 patients were registered, constituting the prospective population described in this report. This population was calculated to correspond to 79% of the expected number of newly diagnosed myeloma patients under 60 years old within the participating regions. Of the 397 registered patients 313 were included in a specified treatment protocol, constituting the intensive therapy group. The treatment protocol has been described in detail previously.[2] Briefly, the treatment consisted of four phases; induction with vincristine, doxorubicin and dexamethasone (VAD), blood stem cell mobilization with cyclophosphamide and granulocyte colony-stimulating factor (G-CSF), high-dose melphalan with stem cell support and interferon maintenance therapy.

Historic population

The historic population, used for comparison of survival with the prospective population, was identified from five previous, prospective, population-based Nordic studies on conventional chemotherapy. Details of the historic population have been presented previously.[2,3] Briefly, a total of 313 patients younger than 60 years were registered in the historic population. This population was calculated to represent 76% of the expected number of cases. The records of all the patients were reviewed and updated. Thirty-nine patients were retrospectively judged not to fulfil the eligibility criteria for intensive therapy stated in the NMSG #5/94 protocol.[2] The remaining 274 patients constituted the historic control group, used for comparison of survival with the intensive therapy group. Approximately 90% of the patients in the historic population received up-front therapy with melphalan and prednisone.

Definitions

The diagnostic and eligibility criteria for intensive therapy used in the NMSG #5/94 study have been described in detail previously.[2] Complete response was defined by the disappearance of M-protein from serum and urine, as detected by agarose gel electrophoresis, and less than 5% plasma cells in a bone marrow aspirate. Partial response was defined by a reduction of at least 50% in the initial serum M-protein concentration and a reduction of light chain proteinuria to less than 0.2 g/24h. A minor response was defined by a 25-50% reduction of the initial serum M-protein concentration and a reduction of the light chain proteinuria by at least 50% but exceeding 0.2 g/24h. To fulfill the criteria for complete, partial or minor response the patients were not allowed to have any other signs of myeloma progression, such as persisting hypercalcemia or progressive renal insufficiency, skeletal disease or bone marrow insufficiency due to plasma cell infiltration. Progression was defined by a confirmed increase of the serum M-protein concentration by more than 25% (but to at least 10 g/L) from the level at the time of best response, or an increase of light chain proteinuria to more than 1.0 g/24h, or by other unequivocal signs of disease progression, such as hypercalcemia, progressive skeletal disease or soft tissue plasmacytoma. Progression, death from any cause without preceding progression, and occurrence of a secondary malignancy were considered as events. Event-free and total survival were calculated from the start of initial therapy, from the time of transplantation, as a landmark analysis or from the time of relapse, depending on the analysis performed.

Statistics

Event-free and total survival were calculated according to the Kaplan-Meier method, and differences in survival between groups were compared by the log-rank test. The Cox proportional hazard regression model was used to estimate the prognostic importance of different variables. The following variables were included in the analyses; (i) variables present at diagnosis: age, percentage of bone marrow plasma cells, hemoglobin concentration, white blood cell count, platelet count, lactate dehydrogenase (LDH), creatinine, albumin, calcium, β-2-microglobulin (all entered as continuous variables), gender (male versus female), M-protein class (IgG versus other; IgA versus other; pure light chain versus other), M-protein size (IgG >70 g/L or IgA >50 g/L or IgD >10 g/L or urinary light chains >12 g/24h versus lower), osteolytic lesions (advanced versus other), performance status according to WHO (0-1 versus 2-4); (ii) other variables: time from start of VAD to transplantation (continuous), best response to therapy (complete versus not complete response), time from transplantation to relapse (continuous). In the multivariate analyses a forward stepwise variable selection was used. Variables with prognostic importance according to the multivariate analyses are presented in the order they entered the model. All analyses were performed on an intention-to-treat basis.

Results

Prospective population versus historic population

The prospective population comprised all of the 397 registered patients. Of these, 313 (79%) were included in the NMSG intensive therapy protocol. Reasons for non-inclusion are summarized in Table 1. In total, 346 of the 397 registered patients (87%) entered protocols in which high-dose therapy with autologous stem cell transplantation was an intended part of the up-front therapy. Survival for the prospective and the conventionally treated historic population is shown in Figure 1. Survival at 5 years was 50% (95%CI 45-55%) and median survival 60 months for the prospective population versus 34% (95%CI 29-40%) and 39 months, respectively, for the historic population (risk ratio (RR) 1.44, 95%CI 1.19-1.74; p=0.0002).

Intensive therapy group versus historic control group

The intensive therapy group comprised the 313 patients included in the NMSG #5/94 therapy protocol. Stem cell transplantation was performed in 247 (79%) of the included patients. The reasons for not being transplanted are summarized in Table 1 (five of these patients underwent autologous transplantation at a later stage of their disease). The total response rate was 87% (34% complete, 42% partial and 11% minor responses). Event-free survival at 5 years was 23% (95%CI 18-28%) and the median event-free survival from start of therapy was 28 months. Survival for the intensive therapy group and the conventionally treated historic con-

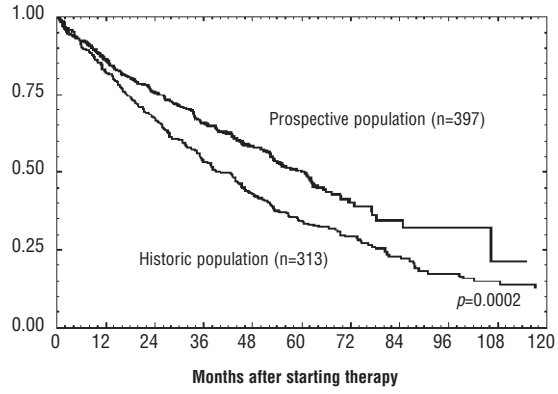

Figure 1. Survival for all the registered patients in the prospective and historic populations.

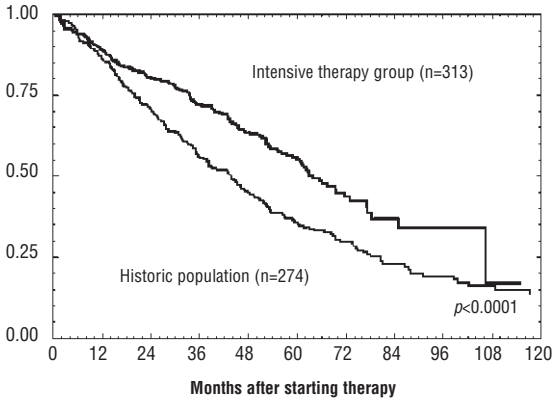

Figure 2. Survival for the intensive therapy group and the historic control group.

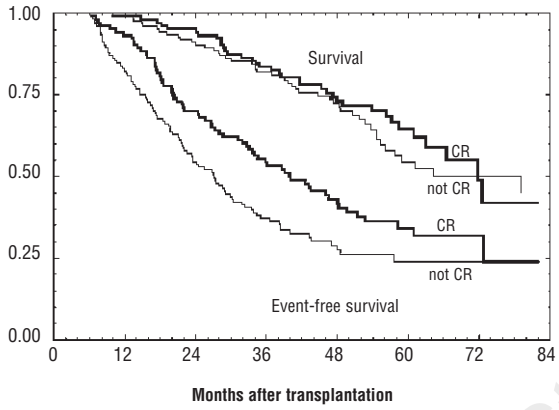

Figure 3. Landmark analysis at 6 months post-transplant of event-free and total survival comparing patients who attained or did not attain a complete response (CR) after transplantation. Attaining a complete response was significantly associated with prolonged event-free survival (median 40 vs. 27 months; p=0.01) but not with prolonged survival (median 71 vs. 64 months; p=0.54).

Table 1. Reasons for non-inclusion of registered patients in the intensive therapy protocol and completion of assigned therapy.

Number of registered patients (=prospective population)	397
Not eligible for intensive therapy for medical reasons	24*
Physician's choice to refrain from intensive therapy	11
Patient's choice to refrain from intensive therapy	16
Inclusion in intensive therapy protocols other than NMSG #5/94	33
Number of included patients (=intensive therapy group)	313
Not transplanted for medical reasons	48
Patient and/or physician choice to refrain from transplantation	18
Number of transplanted patients (=transplanted group)	247

**Due to bad performance status including refractory uremia (n=9), severe coincident heart or lung disease (n=6), other active malignancy (n=3), other severe coincident disease (n=3), psychiatric disease or abuse (n=3).*

trol group is shown in Figure 2. Survival at 5 years was 55% (95%CI 49-61%) and median survival 63 months for the intensive therapy group versus 35% (95%CI 29-41%) and 44 months for the historic control group (RR 1.58, 95%CI 1.28-1.97; p<0.0001). In a multivariate analysis, four of the variables available at diagnosis (lactate dehydrogenase, β-2-microglobulin, hemoglobin and platelet count) were found to be significantly associated with event-free survival while three variables (β-2-microglobulin, hemoglobin and lactate dehydrogenase) had prognostic importance for survival in the intensive therapy group.

Transplanted group

The transplanted group comprised the 247 patients in the intensive therapy group who were actually transplanted as a part of their up-front therapy. Transplantation was performed at a median of 5 months after the start of VAD therapy; 241 transplants were autologous, one syngeneic and five allogeneic with cells from an HLA-identical sibling donor after full conditioning. Treatment with interferon α-2b was started in 88% of the eligible patients at a median time of 3.0 (range 1.2-9.1) months after the autologous transplant. More than 70% of the eligible, non-relapsing patients continued to receive interferon (median dose 6 MU/week) for at least 2 years. At the time of transplantation 13% had attained a complete response, a 60% partial response and 17% a minor response. The response rate after transplantation was 43% for complete, 47% for partial and 8% for minor responses. There were four transplant-related deaths (all caused by infections after autologous transplantation) resulting in a transplant-related mortality at 100 days of 1.6%. Three patients died more than 100 days post-transplant without preceding myeloma progression (two from therapy-related acute myeloid leukemia and one from myocardial infarction) resulting in a total non-relapse mortality of 2.8%. Event-free survival at 5 years calculated from the date of transplantation was 27% (95%CI 21-33%) and survival at 5 years 57% (95%CI 50-64%). The median event-free and total survival after transplantation was 29 and 66 months, respectively.

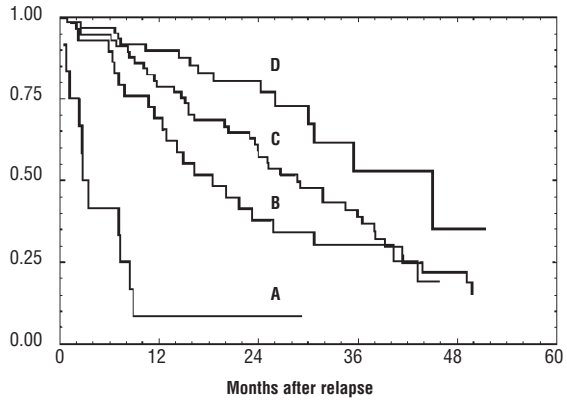

Figure 4. Survival after relapse for patients relapsing; A: within 6 months; B: 6-12 months; C: 12-24 months; D: more than 24 months after transplantation.

Prognosis according to the degree of response after transplantation

To evaluate the importance of attaining a complete response after transplantation a landmark analysis was performed at 6 months after transplantation. This analysis considered 231 patients, excluding the 16 patients who had experienced an event within 6 months after transplantation. A complete response had been achieved by 45% of the eligible patients. Attaining complete remission was found to be significantly associated with a prolonged event-free survival (Figure 3) and it remained as an independent factor (RR 0.68, 95%CI 0.49-0.94; p=0.02) when included in a multivariate analysis with the other variables independently associated with event-free survival. Attaining a complete response was also associated with a prolonged time to symptomatic relapse (defined as the start of relapse therapy) but the difference was less pronounced (median 42 versus 33 months; p=0.03). In contrast, attaining a complete response was not associated with a significantly improved survival (Figure 3) and this observation persisted (RR 0.81, 95%CI 0.50-1.31; p=0.38) in a multivariate analysis comprising the other variables independently associated with survival.

Prognosis of patients progressing after transplantation

Of the 247 patients who underwent stem cell transplantation 162 have progressed. The median time to progression for these 162 patients was 25 months from the start of therapy and 20 months from transplantation. The median survival after progression was 29 months. Ninety-two patients have died, three while responding to salvage therapy (two from complications after allogeneic stem cell transplantation and one from suicide) and the remaining 89 from disease progression. Two variables were significantly associated with survival after progression; time from transplantation to progression and gender (male better). Patients progressing within 6, 6-12, 12-24 and more than 24 months post-transplant had a median survival after progression of 3, 17, 28 and 37 months, respectively (Figure 4).

Patterns of relapse

Based on a modification of a model presented by Alegre *et al.*[4] there were four patterns of relapse: (i) insidious form, 31% of relapses (increase of monoclonal component in serum and urine with no clinical manifestations at the start of relapse therapy or up to 100 days after a biochemically defined relapse); (ii) classical form, 51% of relapses (increase in monoclonal component along with clinical symptoms within 100 days after a biochemically defined relapse; (iii) plasmacytoma form, 14% of relapses (bone marrow or extramedullar plasmacytoma, with minor or no other signs of relapse); (iv) transformed disease, 4% of relapses (plasmacytic leukemia, immunoblastic lymphoma). No association was found between the pattern of relapse and any of the clinical characteristics at the time of diagnosis. The insidious form of relapse was significantly less common in patients who had attained complete response after transplantation than in patients who had not (17% versus 40% of the relapses, respectively). Accordingly, a larger fraction of the patients who relapsed from complete response had symptomatic disease at the time of relapse, while a smoldering type of relapse was more common in patients relapsing from a non-complete response. Patients who relapsed with transformed disease had a significantly shorter duration of first response after transplantation (median 3 months) compared to patients relapsing with an insidious (median 20 months), classical (median 20 months) or plasmacytoma (median 24 months) form.

Survival after relapse was longest in patients with the insidious form (median 39 months) and shortest in patients with transformed disease (median 2 months). There was no significant difference in survival after relapse between patients with the classical form of relapse (median 24 months) and those with the plasmacytoma form (median 15 months). Patients with the classical form of relapse were subdivided into two groups; those with skeletal clinical symptoms only at relapse (n=46) and those with additional symptoms such as cytopenias, hypercalcemia, renal insufficiency, etc. (n=37). Patients with only skeletal symptoms had a median survival after relapse of 30 months, while those with additional symptoms had a significantly shorter median survival of 18 months.

The median survival after initiation of relapse therapy was 28 months for patients relapsing with the insidious form, 20 months for patients with the classical form, 15 months for patients with the plasmacytoma form and 2 months for patients with transformed disease at relapse.

Treatment of relapse

Relapse therapy was not regulated in the NMSG #5/94 protocol. Therefore, a substantial number of dif-

ferent regimens were used for the treatment of first relapse. Also, a number of patients who did not respond to the first regimen used went on to receive alternative regimens. Of the 162 patients who relapsed, 156 were evaluable for response after relapse therapy (three asymptomatic patients had not started relapse therapy and three were too early to evaluate). Six patients (4%) attained a complete response, 60 (38%) a partial response and 43 (28%) a minor response to therapy used to treat first relapse. Accordingly, 47 patients (30%) did not respond to salvage therapy. A response to relapse therapy was important for survival after relapse. Patients with a complete or partial response to relapse therapy had a median survival of 36 months and patients with a minor response 37 months, while non-responders had a median survival of 8 months after relapse. The median survival after start of relapse therapy was 33 months for complete and partial responders, 26 months for minor responders and 7 months for non-responding patients.

Table 2 shows the therapy regimens used to treat first relapse after transplantation. Overall, melphalan-based (e.g. melphalan and prednisone) and steroid-based (e.g. VAD) regimens were the most commonly used. Thalidomide-based regimens were not very commonly used because the majority of the patients received relapse therapy before the recognition of thalidomide as an anti-myeloma agent. Twelve patients underwent a new autologous transplantation as their first relapse therapy, and three patients underwent allogeneic stem cell transplantation. There was no association between the duration of the first response and the choice of first relapse regimen. Responses were achieved with all types of relapse regimens used but no comparisons between the different regimens were performed due to the heterogeneity of the material.

Sixty-one patients have been treated for subsequent relapses. Here, thalidomide-based regimens were the most commonly used. Another five patients underwent a new autologous transplantation and three patients underwent an allogeneic transplantation for treatment of subsequent relapse.

Table 2. Regimens used to treat first relapse after transplantation.

Regimen	*Proportion of patients*	*Response rate**
Melphalan-based, e.g. MP	49%	59%
Steroid-based, e.g. VAD	34%	46%
Irradiation only	10%	Not applicable
Polychemotherapy	10%	19%
Thalidomide-based	8%	67%
Cyclophosphamide-based	5%	25%
Autologous transplantation	8%	83%
Allogeneic transplantation	2%	100%

**At least a minor response to the respective regimen either used as first line salvage therapy or as a subsequent regimen to treat first relapse.*

Discussion

Randomized studies[5-7] and case-controlled analysis[8] have shown that intensive therapy with autologous stem cell transplantation improves survival compared to conventional chemotherapy in newly diagnosed younger myeloma patients. Here we confirm this finding in a population-based setting with long-term follow-up (median 7 years). Our results indicate that the introduction of intensive therapy as standard up-front treatment instead of conventional melphalan and prednisone has resulted in a prolongation of median survival for the whole population of symptomatic myeloma patients under 60 years old by about 1.5 years. However, it should be noted that in recently published randomized studies in which more intense therapy was given to the patients in the conventional arm no survival advantage was found for patients in the transplantation arm.[9-11] Only a minority of transplanted patients achieve durable remissions, and treatment of relapse is therefore a substantial part of the management of these patients. The relapse situation is challenging for the physician. First, the pattern of relapse after high-dose therapy is very heterogeneous, as seen in our study as well as in other similar published studies.[4,12] Second, an increasing number of treatment options are available, but there is a lack of comparative trials between different regimens and no *golden standard* for relapse therapy has been established. In this study, in which most patients received their first salvage therapy prior to the era of new anti-myeloma agents, conventional melphalan and prednisone and VAD were the most commonly used regimens for treating relapse; however, a large number of different regimens were used, reflecting different treatment traditions and the need for individualization of treatment according to each patient's need. The pattern of relapse and time to progression both reflect the underlying biology of the disease and predict the effect of conventional chemotherapy. Patients with *good risk* relapse (insidious form, classical form with only skeletal events and patients with a long-lasting first response) most likely respond well to common chemotherapy such as melphalan- or steroid-based regimens or irradiation. The value of new *non-cytotoxic* anti-myeloma agents such as thalidomide,[13] bortezomib,[14] lenalidomide,[15] CC-4047[16] and arsenic trioxide[17] should be tested in these patients against conventional therapy in randomized trials. In patients with an aggressive relapse pattern (transformed disease, classical form with multiple symptoms and patients with a short first response) the results with conventional chemotherapy are poor and experimental approaches including new agents are warranted.

Survival is considered to be the most robust end-point in randomized trials evaluating new treatment approaches. However, the use of survival as an end-

point has become difficult because of the increasing complexity of treatment and the advent of several new anti-myeloma agents needing evaluation. The increasing number of treatment options after relapse makes it more difficult to interpret the results of studies on initial therapy. It has been suggested that response rate and event-free survival should be used as surrogate end-points for survival, thereby enabling a more rapid evaluation of new treatment options used in the up-front setting. Conflicting results have been presented concerning the importance of attaining a complete response for obtaining prolonged event-free survival and overall survival.[5-6, 18-21] In our analysis we found that attaining a complete response was associated with prolonged event-free survival but not total survival. One explanation for this finding may be that the definition of progression that we used in this study does not correspond to an event of clinical importance and that the definition favors complete responders in evaluating event-free survival. However, it is also possible that patients relapsing from complete response have a more aggressive clone emerging than that of patients progressing from non-complete response. It is obvious that the definition of relapse used today results in a very heterogeneous pattern with highly variable prognosis after relapse. Therefore, both complete response rate and event-free survival must be considered as unreliable surrogate markers for survival in clinical studies. However, the attainment of a stable response of any degree is of value for the patient if it is associated with an improved quality of life. Myeloma is still, in the vast majority of patients, an incurable disease and an improvement in quality of life is of primary importance in addition to prolongation of survival. Therefore, quality of life measurements should be used in all trials, especially when using primary end-points other than survival.

The management of relapse after autologous transplantation is a challenge for physicians. The pattern of relapse and the time to progression after transplantation are two important clinical factors to consider when deciding salvage therapy.

SL is primarily responsible for the NMSG #5/94 study, responsible for the paper and for the creation of all the Tables and Figures in the paper; MH, IT, JW, PG and FW were all members of the steering group of this study. They are listed in the order of their contribution to the paper.

Lucia Ahlberg, Kristina Carlson, Ilse Christiansen, Inger Marie Dahl, Karin Forsberg, Lorentz Brinch, Jens Hammerström, Hans E Johnsen, Lene Meldgaard Knudsen, Olle Linder, Ulf-Henrik Mellqvist, Ingerid Nesthus and Johann Lanng Nielsen were all regional coordinators for the study and responsible for data collection within their regions. They are listed in alphabetical order.

All investigators participated in the interpretation of the results and the preparation of the manuscript.

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References

1. Gratwohl A, Baldomero H, Passweg J, Frassoni, F, Niederwieser D, Schmitz N, et al. Hematopoietic stem cell transplantation for haematological malignancies in Europe. Leukemia 2003;17:941-59.
2. Lenhoff S, Hjorth M, Holmberg E, Turesson I, Westin J, Nielsen JL, et al. Impact on survival of high-dose therapy with autologous stem cell support in patients younger than 60 years with newly diagnosed multiple myeloma: a population-based study. Nordic Myeloma Study Group. Blood 2000;95:7-11.
3. Hjorth M, Holmberg E, Rödjer S, Turesson I, Westin J, Wisløff F. Survival in conventionally treated younger (<60 years) multiple myeloma patients: no improvement during two decades. Eur J Haematol 1999; 62:271-7.
4. Alegre A, Granda A, Martinez-Chamorro C, Diaz-Mediavilla J, Martinez R, Garcia-Larana J, et al. Different patterns of relapse after autologous peripheral blood stem cell transplantation in multiple myeloma: clinical results of 280 cases from the Spanish Registry. Haematologica 2002;87:609-14.
5. Attal M, Harousseau JL, Stoppa AM, Sotto JJ, Fuzibet JG, Rossi JF, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. N Engl J Med 1996; 335: 91-7.
6. Child JA, Morgan GJ, Davies FE, Owen RG, Bell SE, Hawkins K, et al. High-dose chemotherapy with hematopoietic stem-cell rescues for multiple myeloma. N Engl J Med 2003;348:1875-83.
7. Palumbo A, Bringhen S, Petrucci M, Musto P, Rossini F, Nunzi M, et al. Intermediate-dose melphalan improves survival of myeloma patients aged 50 to 70: results of a randomized controlled trial. Blood 2004; 104:3052-7.
8. Barlogie B, Jagannath S, Vesole DH, Naucke S, Cheson B, Mattox S, et al. Superiority of tandem autologous transplantation over standard therapy for previously untreated multiple myeloma. Blood 1997;89:789-93.
9. Blade J, Rosinol L, Sureda A, Ribera JM, Diaz-Mediavilla J, Garcia-Larana J, et al. High-dose therapy intensification compared with continued standard chemotherapy in multiple myeloma patients responding to the initial chemotherapy: long-term results from a prospective randomized trial from the Spanish cooperative group PETHEMA. Blood 2005;106:3755-9.
10. Fermand JP, Katsahian S, Divine M, Leblond V, Dreyfus F, Macro M, et al. High-dose therapy and autologous blood stem-cell transplantation compared with conventional treatment in myeloma patients aged 55 to 65 years: long-term results of a randomized control trial from the Group Myelome-Autogreffe. J Clin Oncol 2005;23:9227-33.
11. Barlogie B, Kyle RA, Anderson KC, Greipp PR, Lazarus HM, Hurd DD, et al. Standard chemotherapy compared with high-dose chemoradiotherapy for multiple myeloma: final results of phase III US Intergroup Trial S9321. J Clin Oncol 2006;24:929-36.
12. Fassas A, Barlogie B, Ward S, Jagannath S, Vesole D, Mattox S, et al. Survival after relapse following tandem autotransplants in multiple myeloma patients: the University of Arkansas total therapy I experience. Br J Haematol 2003;123:484-9.
13. Singhal S, Mehta J, Desikan R, Ayers D, Roberson P, Eddlemon P, et al. Antitumor activity of thalidomide in refractory multiple myeloma. N Engl J Med 1999;341:1565-71.
14. Richardson PG, Barlogie B, Berenson J, Singhal S, Jagannath S, Irwin D, et al. A phase 2 study of bortezomib in relapsed, refractory myeloma. N Engl J Med 2003; 348:2609-17.
15. Richardson PG, Schlossman RL, Weller E, Hideshima T, Mitsiades C, Davies F, et al. Immunomodulatory drug CC-5013 overcomes drug resistance and is well tolerated in patients with relapsed multiple myeloma. Blood 2002;100:3063-7.
16. Schey, SA, Fields P, Bartlett JB, Clarke IA, Ashan G, Knight RD, et al. Phase I study of an immunomodulatory thalidomide analog, CC-4047, in relapsed or refractory multiple myeloma. J Clin Oncol 2004;22:3269-76.
17. Hussein MA, Saleh M, Ravandi F, Mason J, Rifkin RM, Ellison R. Phase 2 study of arsenic trioxide in patients with relapsed or refractory multiple myeloma. Br J Haematol 2004;125:470-6.
18. Rajkumar SV, Fonseca R, Dispenzieri A. Effect of complete response on outcome following autologous stem cell transplantation for myeloma. Bone Marrow Transplant 2000;9:979-83.
19. Desikan R, Barlogie B, SawyerJ, Ayers D, Tricot G, Badros A, et al. Results of high-dose therapy for 1000 patients with multiple myeloma: durable complete remissions and superior survival in the absence of chromosome 13 abnormalities. Blood 2000; 95:4008-10.
20. Tricot G, Spencer T, Sawyer J, Spoon D, Desikan R, Fassas A, et al. Predicting long-term (> or = 5 years) event-free survival in multiple myeloma patients following planned tandem autotransplants. Br J Haematol 2002; 116:211-7.
21. Attal M, Harousseau JL, Facon T, Guilhot F, Doyen C, Fuzibet JG, et al. Single versus double autologous stem-cell transplantation for multiple myeloma. N Engl J Med 2003; 349:2495-502.