Double versus single high-dose melphalan 200 mg/m^2 and autologous stem cell transplantation for multiple myeloma: a region-based study in 484 patients from the Nordic area

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Abstract

Autologous stem cell transplantation is still considered the standard of care in young patients with multiple myeloma (MM). This disease is the most common indication for high-dose therapy (HDT) supported by hematopoietic stem cell transplantation and much data support the benefit of this procedure. Results of randomized studies are in favor of tandem autologous transplantation although the effect on overall survival is unclear. Based on sequential registration trials in the Nordic area, we aimed to evaluate the outcome of conventional single or double HDT.

During 1994-2000 we registered a total of 484 previously untreated patients under the age of 60 years at diagnosis who on a regional basis initially were treated with single [Trial NMSG #5/94 and #7/98 (N=383)] or double [Trial Huddinge Karolinska Turku Herlev (N=101)] high-dose melphalan (200 mg/m^2) therapy supported by autologous stem cell transplantation.

A complete or very good partial response was achieved by 40% of patients in the single transplant group and 60% of patients in the double transplant group (p=0.0006). The probability of surviving progression free for five years after the diagnosis was 25% (95% CL 18-32%) in the singletransplant group and 46% (95% CL 33-55%) in the double transplant group (p=0.0014). The estimated overall five-year survival rate was 60% in the single transplant group and 64% in the doubletransplant (p=0.9). In a multivariate analysis of variables, including single versus double transplantation, β2 microglobulin level, age, sex and disease stage, only β2 microglobulin level was predictive for overall survival (p>0.0001) and progression free survival (p=0.001). In accordance with these results, a 1:1 case-control matched comparison between double and single transplantation did not identify significant differences in overall and progression free survival.

In this retrospective analysis *up front* double transplantation with melphalan (200 mg/m^2) as compared to single transplantation did not seem to improve the final outcome among patients in the Nordic area. These data are in accordance with recent publications from the Bologna 96 trial indicating that a second transplant should not be recommended up front as standard care.

Introduction

Multiple myeloma (MM) is the second most common hematologic cancer after non-Hodgkin's lymphoma. More than 50,000 patients in Europe alone have MM and about half of these patients are diagnosed when they are younger than 65 years of age, and increasingly detected under the age of 40.

Today, MM is the most common indication for high-dose therapy supported by hematopoietic stem cell transplantation in the world, and more data support the benefit of this procedure. These remarkable results radically altered the disease management in patients below 65 years of age. Thus, stem cell transplantation has been recommended for these patients as part of the initial therapy or at the time of disease progression. However, the median duration of response is short and almost all patients ultimately relapse.[1-9]

The InterGroupe Francophone du Myélome (IFM) took the next logical step and asked if the combination of two cycles of high-dose therapy and hematopoietic stem cell rescue might improve survival. The group assigned 399 patients with untreated MM below 60 years of age to receive VAD (vincristine, adriamycin and dexamethasone) as induction therapy and afterwards assigned these patients randomly to single or double transplantation conditioned by melphalan 140 mg/m^2 and TBI (standard single transplantation) or melphalan 140 mg/m^2 followed by 140 mg/m^2 and TBI (experimental double transplantation).[10] Following a median observation of approximately six years, response rates in the two groups were not significantly different, but the probabilities of event free survival and overall survival were prolonged with a double transplant benefit that had not been evident in early analyses.[10] This important study demonstrates that double transplantation is one of the options for treating myeloma, particularly those younger than 60 years of age who have a suboptimal response to a single transplant.

However, the IFM study has raised a number of questions. First and most important, do the beneficial responses in the double trans-

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Contributions: all authors listed below have approved submission for publication. Further information about the contributions of each partner who participated in this collaborative project is given below. BB assisted in study design and patient data; TWK assisted in data collection, analysis and interpretation; KR, AG, LMK, OJB and SL assisted in study design and patient data; HEJ is corresponding author/guarantor and coordinator, assisted in study design, provision of biomaterial and patient data, data collection, analysis and interpretation, and manuscript preparation.

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plant group reflect the higher total dose of melphalan? In other words, is a single transplant with the use of maximally tolerated doses of melphalan (200 mg/m^2) as effective as a double transplantation strategy with the high dose of melphalan administrated twice?

Second, what should be recommended, as only one of several phase II-III studies has documented an effect on overall survival?[11,12]

Without doubt the IFM study has to be considered the *Proof of Principle* but in the light of the study design, as well as the overall results from other studies, it is still unknown if a second transplant should be recommended in all cases, even if the response to the first transplant has been inferior.

In this unclear situation we now see alternative progress in the treatment of MM by new drugs currently being analyzed in randomized trials. In the near future, ongoing studies will clarify the role of these novel agents, including thalidomide and its analogs, and bortezomib etc., in the context of autologous stem cell transplantation. However, trial designs including consolidation therapy such as that planned by the NMSG may be hampered by a double autologous transplantation strategy, not yet documented to have an effect on survival. Here the Nordic group reports the data analysis of a total of 484 MM patients transplanted from 1994-2000 including double transplantation of 101 patients. The conclusions are based on results from two sequential phase II trials evaluating double transplantation in 4 selected centers (Huddinge, Karolinska, Turku and Herlev) by comparing the outcome with data from 383 single transplanted patients included in trial NMSG #5/94 and #7/98 from the other centers.[1,13,14]

Design and Methods

Approval and patient eligibility

The scientific protocols were reviewed and approved by the regional ethics committees in Denmark, Sweden, Finland and Norway, and all patients gave written informed consent before study entry. Patients less than 60 years of age who had Durie-Salmon stage I with at least one bone lesion, II, or III myeloma were eligible. The criteria for exclusion were prior treatment for myeloma, another cancer, abnormal cardiac function, chronic respiratory disease, abnormal liver function or psychiatric disease.

Design and aims of the program

This study was planned to include previously untreated patients under the age of 60 years at diagnosis who on a regional basis initially were treated with single [Trial NMSG #5/94 and #7/98 (N=383)] or double [Trial HKTH (N=101)] high-dose melphalan (200 mg/m^2) therapy supported by autologous stem cell transplantation. The aim was to evaluate the outcome of conventional single or double HDT.

Double transplant study population: HKTH

From June 1994-June 2000, 101 patients with newly diagnosed myeloma <60 years were entered into a phase II trial evaluating double high-dose melphalan (200 mg/m^2) therapy with autologous stem cell support. This included patients from Huddinge and Karolinska Hospitals in Stockholm, Sweden, Turku University Hospital in Finland, and from June 1997 Herlev University Hospital, Copenhagen in Denmark. This trial covered a population of 3 million. The number of new cases of myeloma <60 years in this population during the study period was estimated to be 200 patients.

Single transplant population NMSG #5/941 and NMSG #7/9814 NMSG #5/94

From March 1994 until June 1997, 122 Swedish patients with newly diagnosed myeloma <60 years were entered into NMSG #5/94 trial evaluating one cycle of high-dose melphalan therapy with autologous stem cell support. One hundred and seven of these were treated according to the specified treatment protocol and received single transplantation. This trial covered a population of 15 million. A total of 348 Nordic patients were reported to the study secretariat. The expected number of new cases of myeloma <60 years in this population during the study period was estimated to be 450. In this trial, a highly significant survival advantage was found for high-dose melphalan therapy, with a prolongation of the median survival from 44 to 62 months.[1]

NMSG #7/98

From January 1998 until June 2000, 452 patients <65 years were registered in a similar trial evaluating high-dose melphalan with autologous stem cell support, and using a matched historical patient group as control. Of these, 276 Swedish, Norwegian and Danish patients aged <65 years were treated according to the specified treatment protocol and received single transplantation. This trial also covered a population of 15 million. A total of 452 patients were reported to the study secretariat. The number of expected new cases of myeloma <65 years in this population during the study period was estimated to be 580. The main purpose of this study was to evaluate the impact of high-dose melphalan therapy in patients aged 60-64 years in a population-based study. Age was found to influence outcome after intensive therapy, which, however, prolonged survival but with less superiority than in younger patients.[14]

Treatment plan

All patients could be treated according to the protocol provided that they were not considered ineligible for the induction therapy. The treatment was divided into 4 phases: (I) induction therapy; (II) peripheral blood stem cell harvest; (III) high-dose therapy with single or double high-dose melphalan 200 mg/m^2 given as a single dose intravenously, followed by stem cell transplantation and (IV) follow-up (described in details in 1). Patients with progressive disease or with emerging contraindications to phases II to III were taken off the treatment protocol.

Diagnostic criteria

The diagnosis of MM was accepted if criteria A+C, A+D, or B+C+D of the following were fulfilled: (A) serum monoclonal component (M-protein) concentration of immunoglobulin (Ig)G > 30 g/L, IgA > 20 g/L, the presence of an M-protein of IgD or IgE regardless of concentration, or Bence-Jones proteinuria > 1 g/24 h; (B) M-protein in serum or urine at a lower concentration than described under A; (C) at least 10% plasma cells in bone marrow aspirate or biopsy-verified plasmacytoma of bone or soft tissue; and (D) osteolytic bone lesions. Only patients with symptomatic disease were registered.

Criteria for response

Complete response was defined as the disappearance of M-protein from serum and urine in agarose gel electrophoresis and < 5% plasma cells in a bone marrow aspirate. Very good partial remission (VGPR) was 90-99% reduction of M-protein. Partial response was defined by at least a 50% reduction of the initial serum M-protein concentration and a reduction of Bence-Jones proteinuria to <0.2 g/24 h. Minor response was defined by a 25-50% reduction of the initial serum M-protein concentration and a reduction in Bence-Jones proteinuria by at least 50% but exceeding 0.2 g/24 h.

No statistically significant differences were observed between the groups at any stage of the treatment with regard to these comparisons. 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 in the serum M-protein concentration by more than 25% from the level at the time of best response, an increase of Bence-Jones proteinuria to more than 1.0 g/24 h, or other unequivocal signs of disease progression, such as hypercalcemia, progressive skeletal disease, or soft-tissue plasmacytoma. Progression, death without progression, and occurrence of a secondary malignancy were all considered as events. Event free and overall survival was calculated from the start of therapy.

Follow-up evaluation

All registered patients were followed until death. Patients were evaluated before the start of phase II and phase III, and thereafter every sixth week.

Statistical analysis

All analyses were performed on treatment received basis and are not an intention-to-treat study. The proportions of patients with a given characteristic were compared using Fisher's exact test for variables with frequency scale and Wilcoxon rank-sum test for the remaining variables. Event free and overall survival rates were calculated according to the Kaplan-Meier method, and survival comparisons between groups were made by the log-rank test. The Cox proportional hazards regression model was used to estimate the prognostic importance of different variables. Age, bone marrow plasma cells, blood hemoglobin, serum calcium, serum creatinine, blood platelets, and serum albumin were included as continuous variables. The following variables were dichotomized: sex (male *vs.* female), stage according to Durie and Salmon (I or II *vs.* III), M-protein class (IgG *vs.* other; IgA *vs.* other; light chains only *vs.* other), and osteolytic bone lesions (none *vs.* limited or advanced). In the multivariate analyses, forward stepwise variable selection was used.

Results

Baseline characteristics at diagnosis

Table 1 shows the base-line clinical and demographic characteristics of the 484 patients entering this analysis. There were no differences between the treatment groups but for disease stage.

Response rates in the collaborative trials

Following the final preparative treatment with high-dose melphalan and autologous stem cell transplantation, the overall rates of complete or very good partial response for patients who actually received a single or a double transplant (Table 2) were in the collaborative trials 60% and 40%, respectively (p=0.0006).

The survival outcome

In the single transplant group, the median follow-up was 34 months (range, 12-115) from the time of transplantation. The median durations of event free, progression free, and overall survival were 33, 33, and 78 months, respectively. The estimated probabilities of event-free, progression free, and overall survival five years after inclusion were 25% (Figure 1a), 26%, and 60% (Figure 1b), respectively. Of the 96 deaths in this group, 85% were attributed to progressive myeloma, 2% related to the transplantation procedure. In the double transplant group, the median follow-up was 48 months (range, 10-108) from the time of transplantation. The median durations of event free, progression free, and overall survival were 46, 46, and 76 months, respectively. The estimated probabilities of event-free, progression free, and overall survival five years after the inclusion were 44% (Figure 1a), 45%, and 64% (Figure 1b), respectively. Of the 33 deaths in this group, 61% were attributed to myeloma, while 3% were related to the transplantation procedure. As compared with single transplantation, double transplantation improved progression free survival (p=0.001) (Figure 1b) whereas overall survival was similar (p=0.9) (Figure 1a).

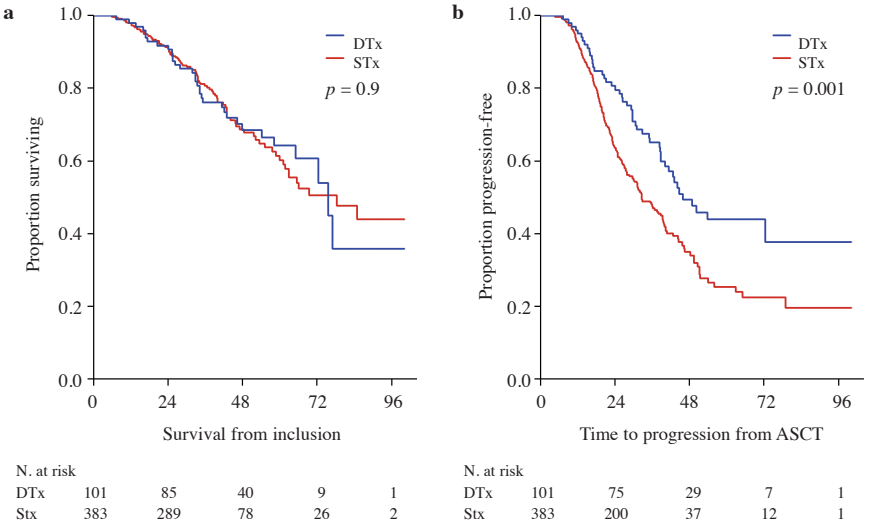

Figure 1. Overall survival (a) and progression free survival (b) following double transplantation in trial HKTH (N=101), compared to single transplantation in NMSG #5/94 plus #7/98 (N=384). The estimated probabilities are shown for double (DTx) and single (STx) transplantation. Tables below the graph indicate patients at risk for the estimate.

Table 1. Base-line characteristics of the patients according to treatment group.

Variable	Double transplantation	Single transplantation	p-value
N	101	383	
Age*	55 years	54 years	0.4#
Sex (female, male)	44/57; (44 and 56%)	151/232; (39 and 61%)	0.5§
β2 microglobulin*	2.8 mg/L	3.4 mg/L	0.1#
Stage I/II/III	12/23/64; (12, 23 and 65%)	16/108/259; (4, 28 and 67%)	0.015§

**Median values; #Mann-Whitney test; §Fisher's exact test.*

Table 2. Comparison between double and single transplantation.

Variable	Double transplantation	Single transplantation	p-value
N (data/missing)	101 (98/3)	383	
CR	56 (57%)	139 (36%)	0.003§
CR + VGPR	59 (60%)	155 (40%)	0.0006§
OS % censored	See Figure 1a	See Figure 1a	0.9*
OS median (years)	6.3	6.5	
PFS % censored	See Figure 1b	See Figure 1b	0.0014*
PFS median (years)	3.8	2.7	

*#Mann-Whitney test; §Fisher's exact test; *Log rank test (See Figure 1a and b)*

Analysis for prognostic variables

In a multivariate analysis of all 484 patients (Table 3), overall survival was significantly related to baseline serum levels of β2 microglobulin (p<0.0001) but not to the maximal response to treatment (p=0.2), not to age (p=0.5), disease stage or treatment assignment (p=0.4).

Case control study comparing double and single transplantation

To illustrate the impact of β2 microglobulin, each double transplanted patient from the study group was matched with one case of a single transplanted patient (N=101) from the corresponding NMSG database, according to β2 microglobulin, age, sex and disease stage in this order. The results are shown in Figure 2 and document no survival benefit.

Treatment-related toxicity

The hematopoietic reconstitution was recognized to be similar in the two groups as expected.[13] There were 2 (0.5%) treatment-related deaths in the single transplant group of 383 patients and 3 (3.0%) in the double transplant group of 101 patients (p=0.06).

Minimal residual disease

In the double transplant group, the number of bone marrow malignant plasma cells 2-3 months post high-dose therapy was estimated by conventional recommended flow cytometry and revealed no significant differences between the levels following the first and the second transplant. The median level of plasma cells was 0.22% and 0.16%, respectively (N=17; p=0.3).

Discussion

Double autologous transplantation regimens have been used to treat myeloma for the past decade, although the advantage over single transplantation is unclear. Despite the favorable results reported by IFM,[10] it remains the case that progressive myeloma will develop in almost 80% of patients within seven years after they have undergone double transplantation. This unclear situation is further extended by progress in the number of new drugs currently being analyzed in randomized trials. In the near future, ongoing studies will clarify the role of inflammatory mediators and proteasome inhibitors in the context of autologous stem cell transplantation. However, trial design including consolidation therapy with new drugs may be hampered by the biased double autologous transplantation up front strategy which has not yet been documented to have an effect on overall survival.[11-12] Among the patients enrolled in the double transplant group in the present study, 23% could not receive their assigned second transplantation and have not been included in this analysis. This number is in accordance with the literature.[10] The most common reasons were a decision for allogeneic transplantation, poor performance status, and poor stem cell collection owing to an insufficient response after the initial VAD treatment.

The risk of life-threatening toxic effects due to double transplantation was a major concern. However, the hematopoietic reconstitution was similar after one or two transplantations[13] but the rates of death caused by toxic effects were increased in the IFM study.

Analysis of the present phase II trials after a median follow-up period of 3-4 years documented significant improved response rates

Table 3. Statistical analysis of variables on overall (OS) and progression free survival.

OS	Univariat		Multivariat	
Variables	RR (95% CI)	p-value	RR (95% CI)	p-value
Single vs. double transplantation	1.0 (0.7-1.5)	0.9	0.8 (0.5-1.3)	0.4
(Log) β2 microglobulin	1.8 (1.5-2.2)	< 0.0001	1.8 (1.4-2.2)	< 0.0001
Age	1.02 (0.99-1.05)	0.3	1.02 (0.99-1.05)	0.3
Sex (Male vs. female)	1.3 (0.9-1.8)	0.1	1.2 (0.8-1.8)	0.4
Stage I, II or III	-	0.3	NI	NI
Stage (II, III vs. I)	2.1 (0.8-5.6)	0.1	1.5 (0.5-5.0)	0.4
Response non-CR vs. CR	1.3 (0.9-1.8)	0.2	NI	NI

PFS	Univariat		Multivariat (N=380)	
Variables	RR (95% CI)	p-value	RR (95% CI)	p-value
Single vs. double transplantation	1.7 (1.2-2.3)	0.0009	1.3 (0.9-1.9)	0.1
(Log) β2 microglobulin	1.3 (1.1-1.6)	0.0006	1.3 (1.1-1.6)	0.001
Age	1.00 (0.98-1.02)	0.9	1.01 (0.98-1.03)	0.6
Sex (Male vs. female)	1.2 (0.9-1.6)	0.1	1.2 (0.9-1.6)	0.2
Stage I, II or III	-	0.06	NI	NI
Stage (II, III vs. I)	2.0 (1.0-3.9)	0.02	1.3(0.6-2.8)	0.5
Response non-CR vs. CR	1.9 (1.4-2.4)	< 0.0001	NI	NI

NI, Variable not included in multivariate analysis

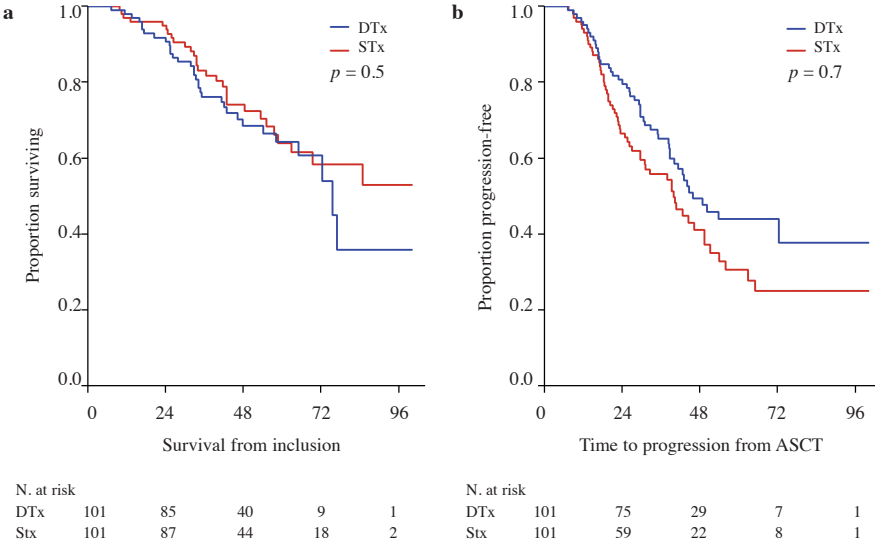

Figure 2. Case control analysis comparing double and single transplantation. Overall survival (a) and progression free survival (b) following double transplantation in trial HKTH was compared to 101 case controlled single transplantations in NMSG #5/94 plus #7/98. The estimated probabilities are shown for double (DTx) and single (STx) transplantation. Tables below the graph indicate patients at risk for the estimate.