Multiple Myeloma: Myeloablative Therapy with Autologous Stem Cell Support *versus* Chemotherapy: A Meta-analysis

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Abstract. *Background: Myeloablative high-dose chemotherapy (HDT) followed by single autologous stem cell transplantation is currently the standard treatment for patients younger than 65 years with newly diagnosed multiple myeloma (MM). Several randomized controlled trials (RCTs) comparing HDT with standard dose therapy (SDT) have shown some benefit in overall survival (OS) and progression-free survival (PFS), whereas other RCTs did not confirm this finding. In this study we attempted to analyze the current data in terms of the endpoints OS and PFS. Materials and Methods: We searched PubMed, Embase, abstracts of former ASH meetings and ClinicalTrials.gov, as well as bibliographies of included trials, and recent reviews from September 2009 until May 2010. Amongst the 3,484 results in this search, we identified 10 RCTs comparing HDT with SDT on an intention-to-treat-basis. Treatment characteristics and outcomes of OS and PFS were reported. We investigated statistical heterogenity and publication bias and performed subgroup analyses. Results: Nine RCTs including 2,600 patients were fully analyzed. Patients undergoing HDT with stem cell transplantation had a significant PFS benefit (hazard ratio=0.73; 95% CI=0.56-0.95; p=0.02) but no OS benefit (HR 0.90; 95% CI 0.74-1.10; p=0.32) as compared to patients undergoing SDT. Conclusion: Although there is only a trend of OS benefit with HDT, it is currently still the first line treatment. Additional data from ongoing clinical trials and new studies using novel agents such as thalidomide, lenalidomide and bortezomib are warranted to finally evaluate the role of HDT in the treatment management of patients with newly diagnosed MM.*

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Key Words: Myeloma, transplantation, stem cell, meta-analysis, myeloablative high-dose chemotherapy.

Multiple myeloma (MM) is a malignant disease of plasma cells accumulating in the bone marrow, which produce immunoglobulin or immunoglobulin light chains. The main symptoms are osteolysis, renal insufficiency, anaemia and infection. At diagnosis, they may vary from changes of the blood count to severe bone lesions of the spinal cord. In most cases, the disease is diagnosed between the ages of 65 and 70 years. MM is one of the most common haematological disorders and has had a poor prognosis for many decades (1). In recent years the introduction of novel agents like thalidomide, lenalidomide and bortezomib has led to some improvement in overall survival (OS) and progression-free survival (PFS). Myeloablative high-dose chemotherapy (HDT) followed by single autologous stem cell transplantation is currently the standard treatment for patients younger than 65 years with newly diagnosed MM (2) and is recommended by the National Comprehensive Cancer Network (NCCN) (3). Several randomized controlled trials (RCTs) (4-6) comparing HDT with standard-dose therapy (SDT) have shown some benefit in OS and PFS, whereas other RCTs did not confirm this finding (7-9). Koreth *et al*. (10) performed a meta-analysis summarizing the existing data of the RCTs including 2,411 patients. These authors found a significant superiority for HDT in PFS but not in OS. Since new data have been published recently, we attempted to re-analyze the current data in terms of the endpoints OS and PFS.

Materials and Methods

Data sources. We analyzed PubMed, Embase, the registry of abstracts of former meetings of the American Society of Hematology (ASH), as well as the registry of clinical trials provided by the U.S. National Ministries of Health, ClinicalTrials.gov. The search included the terms '*myeloma*' combined with '*transplant*' or '*high-dose*' or '*myeloablative*'. The search was restricted to RCTs. Furthermore, we searched bibliographies of included trials and recent reviews (1, 11), the meta-analysis of Koreth *et al*. (10) and one older meta-analysis (12) to find further relevant RCTs. Amongst the 3,484 results we found nine RCTs that met the inclusion criteria given below, but no RCTs additional to the ones of Koreth *et al*.

Table I. *Study design*.

Study (Author)	Power	Follow-up (months)	No. of centers	Country	Randomization	Dropout after randomization	
						SDT	HDT
IFM90 (Attal)	80% to detect if probability of 5-year OS was 50% (HDT) *vs*. 10% (SDT)	SDT: 37 *vs*. HDT 41	33	France, Belgium	Upfront	0%	26%
MAG90 (Fermand)	80% to detect a 20% mortality reduction with early HDT compared with late HDT	58	14	France	Upfront	0%	2%
MAG91 (Fermand)	80% to detect OS benefit with HDT (HR 0.60) *vs*. SDT	120	14	France	Upfront	0%	24%
MRC7 (Child)	80% to detect a 10% OS improvement with HDT (710 patients)	SDT: 32 *vs*. HDT 40	83	UK, New Zealand	Upfront	2%	25%
S9321 (Barlogie)	81% to detect a survival improvement of 33%	76	NR	USA	After induction	<1%	1%
PETHEMA (Bladé)	NR	56	29	Spain	After induction, only responders	11%	
HOVON24 (Sonneveld)	80% to detect an increase in 2-year EFS from 40% to 55%	92	46	Netherlands, Belgium	After induction	1%	1%
M97G (Palumbo)	To detect a statistically significant increase of 20% in EFS at 2 years (240 patients)	SDT: 39 *vs*. HDT: 41	18	Italy	Upfront	4%	2%
IFM99-06 (Facon)	80% to detect an increase of survival time of 18 months (at 500 patients)	52	73	France, Belgium, Switzerland	Upfront	6%/2%	4%

EFS: Event-free survival; HDT: high-dose therapy; SDT: standard-dose therapy; HR: hazard ratio; NR: not reported; OS: overall survival.

Inclusion criteria. Studies were required to be prospective randomized trials with a control arm and to have compared high-dose chemotherapy (HDT) including autologous bone marrow transplantation with standard-dose chemotherapy (SDT). In the HDT arm, any kind of myeloablative therapy was accepted. As common during the time, trials using total body irradiation (TBI) in the HDT arm were also accepted. Inclusion was restricted to studies recruiting only newly diagnosed patients with untreated multiple myeloma. Hazard ratios (HRs) of OS and PFS, or data to calculate them had to be provided.

Data extraction. Data extracted from the trials are summarized in Tables I-III. We collected data on: name of first author, start of enrollment, number of participants and therapy in both arms and entry criteria. We also listed characteristics of the patients included: median age, beta-2-microglobulin and, as reported, either Durie-Salmon stage (13) or stage according to the International Staging System (14). In terms of the results, we extracted effects on OS and PFS, as well as the rate of treatment-related mortality (TRM) and complete remission (CR). To evaluate the quality of studies, we analysed their power, the fraction of patients receiving off-protocol salvage therapy, the duration of follow-up, the countries of included centres and rate of drop-out after randomisation. Following the example of Koreth *et al*., we adhered to common guidelines for quality control in meta-analysis (15).

Data analysis. Data analysis was performed using the open source programming software R (see the Comprehensive R Archive Network (CRAN) at http://cran.R-project.org). The HRs with 95% confidence intervals (CI) of all studies for OS and PFS were illustrated by a forest plot. In calculating the combined HRs, the random effects model was applied. Three subgroup analyses with the application of one of the following exclusion criteria were carried out: studies with less than four years follow-up (excluded in 'long follow up'), non-standard studies (explained below), studies using the application of TBI. We wanted to investigate this last subgroup because a randomised controlled trial by Moreau *et al*. showed benefit for treatment of HDT without TBI compared to HDT combined with TBI (16). Furthermore, we examined statistical heterogeneity with the Q statistic and judged publication bias by a funnel plot (17).

Results

Included trials. In our search, we found 3,484 results. After title/abstract review, we considered 3,321 publications to be definitely irrelevant. Amongst the remaining 163 studies, we found 9 RCTs that met all inclusion criteria. The main reasons for exclusion were: non-RCT, lack of one arm, or addressing different questions other than HDT *vs*. SDT. The following RCTs met inclusion criteria but were excluded in a subgroup-analysis, because they were considered as 'non-standard': The MAG 90 trial (18) was excluded for including a per-protocol rescue treatment with HDT and stem cell transplantation for the standard arm. Patients in this arm started with a different induction regimen (VMCP: vincristine, melphalan, cyclophosphamide and prednisone *vs*. VAMP: vincristine, doxorubicine, methylprednisolone) and were treated like the high-dose arm at the time of disease progression. The trial was accepted because stem cell transplantation was only a rescue-treatment, in part also used in other trials. The HOVON 24 trial

Table II. *Study and patients characeristics*.

Study (Author)	Start	Participants	SDT	HDT	DS III/ ISS III	Age (years): Median (Range)	β-2-Micro-globulin
IFM 90 (Attal)	1990	200	VMCP/BVAP	VMCP/BVAP → Mel 140 + 8 Gy TBI	0.75	57 (<65)	4.8 mg/l
MAG 90 (Fermand)	1990	185	VMCP/(VAMP + HDT at progression)	VAMP → Lo + VP + Cy + Mel 140 + 12 Gy TBI	0.84	48 (<56)	3.8 mg/l
MAG 91 (Fermand)	1991	190	VMCP/(VAMP at progression)	VAMPC → Mel 200/ Mel140 + Bu	0.81	60 (55-65)	3.1 mg/l
MRC7 (Child)	1993	401	ABCM	VAMPC → Mel 200/ Mel 140 + TBI (4%)	NR	55 (33-66)	>4.0 mg/l: 62%
S9321 (Barlogie)	1993	516	VAD --> VBMCP	VAD → Mel 140 + 12 Gy TBI	67%; ISS III: 31%	54 (25-70)	>6 mg/l: 31%
PETHEMA (Bladé)	1994	164	VBMCP/VBAD	VBMCP / VBAD → Mel 200 / Mel 140 + 12 Gy TBI (30%)	NR	56 (<65)	>4.1 mg/l: 66%
HOVON 24 (Sonneveld)	1995	303	VAD → 2 x Mel 70	VAD → 2 x Mel 70 --> Cy 120 + 9 Gy TBI	0.75	56 (32-65)	3 mg/l
M97G (Palumbo)	1997	194	MP	VAD → 2 x Mel 100	0.62	64 (51-70)	2.9 mg/l
IFM 99-06 (Facon)	2000	447	MP/ MPT	VAD → 2 x Mel 100	ISS III: 31%	NR (65-75)	>3.5 mg/dl: 61%

ABCM: Doxorubicine, carmustine, cyclophosphamide, melphalan. Bu: Busulphan. Cy: Cyclophosphamide. DS: Durie-Salmon-Stage. ISS: International Staging System. Lo: Lomustine Mel: Melphalan. MP: Melphalan, prednisone. MPT: Melphalan, prednisone, thalidomide. NR: Not reported. TBI: Total body irradiation. VAD: Vincristine, doxorubicine, dexamethasone. VAMP: Vincristine, doxorubicine, methylprednisolone. VAMPC: Vincristine, doxorubicine, methylprednisolone, cyclophasphamide. VBAD: Vincristine, carmustine, doxorubicine, dexamethasone. VBMCP: Vincristine, carmustine, melphalan, cyclophasphamide, prednisone. VMCP: Vincristine, melphalan, cyclophasphamide, prednisone. VP: Etoposide.

(19) used a relatively aggressive induction regime for both arms (VAD: vincristine, doxorubicine, dexamethasone followed by cyclophosphamide followed by melphalan 70 mg/m^2 allocated twice at six-to-eight-weeks intervals). Myeloablative treatment in the HDT arm was cyclophosphamide + TBI. This treatment might have had an impact on outcomes such as the need for rescue treatment in the SDT arm. M97G (6) focused on patients ineligible for standard stem cell transplantation treatment. Therefore, patients were older (up to 70 years) and a reduced dose of melphalan 100 mg/m^2 allocated twice at two-month intervals (Mel 100×2) at each time followed by stem cell transplantation (tandem transplant) was scheduled. Furthermore, the two arms received different induction regimens as that was state of the art at the start of the trial. As the total dose of melphalan was similar to that of other trials, we included the study in the initial analysis. Another 'intermediate-dose' trial was IFM 99-06 (20): patients enrolled were ineligible for regular HDT regimen and aged between 65 and 75 years. The HDT arm used melphalan 100 mg/m^2 allocated twice at two-month intervals (Mel100×2) and there were two standard arms (MPT: melphalan, prednisone, thalidomide *vs*. MP: melphalan, prednisone). As we did not consider it as clinically meaningful to combine the two standard arms (21), we calculated outcomes separately. As a standard of analyses, Mel100×2 *vs*. MPT was considered. Using the MP arm instead did not result in clinically relevant difference in combined HRs. Hazard estimates for OS ranged from 0.40 (preferring HDT) to 1.45 (preferring SDT). Hazard estimates for PFS ranged from 0.42 to 1.69. The Q statistic showed significant heterogeneity: p=0.002 for OS and p<0.001 for PFS. No significant heterogeneity was present in the subgroup analyses of OS when only trials with 'standard protoco' or with 'long follow-up' were considered. With regard to PFS, only the soubgroup of trials with 'standard protocol' showed no significant heterogeneity. The funnel plot gave no indication of publication bias.

Combined HRs for OS with HDT. The combined HR for OS gained from the nine trials was 0.90 (95% CI=0.74-1.10). There was no statistically significant OS benefit with HDT. The same result applied to the subgroups 'no TBI' (HR=0.84; 95% CI=0.50-1.39) and 'long follow-up' (HR=1.06; 95% CI=0.94-1.20). The subgroup 'standard protocols' showed a trend for an OS benefit with HDT (HR=0.87; 95% CI=0.74-1.02). Removing every single trial from the analysis in turn did not lead to relevant differences in the effects (not illustrated). Results are illustrated in Figure 1.

Combined HRs for PFS with HDT. The publications of the nine trials gave information on PFS or event-free-survival. As the definition of both terms is similar, the results were summarized as PFS. The combined HR for the nine studies was 0.73 (95%

Table III. *Entry criteria and results*.

Study (Author)	Entry criteria	Response rate (CR)		TRM		Results: Benefit?		Salvage HDT therapy
		SDT	HDT	SDT	HDT	OS	PFS/EFS	
IFM 90 (Attal)	Untreated MM, DSS II or III, no chemo- or radiotherapy, no cardiac, pulmonal or hepatic dysfunction, no psychiatric disease	0.05	0.22	NR	0.02	Yes	Yes	0.09
MAG 90 (Fermand)	Symptomatic MM, <56 years, no prior chemo- or radiotherapy, no renal, cardiac, hepatic or pulmonal dysfunction	0.05	0.19	0.14	0.1	No	Yes	0.78
MAG 91 (Fermand)	Untreated symptomatic MM, no chemo- or radiotherapy, no renal, cardiac, hepatic or pulmonal dysfunction	0.04	0.06	0.02	0.05	No	Yes	0.22
MRC7 (Child)	Untreated MM, <65 years, met MRC criteria, suitable for HDT	0.08	0.44	NR	0.03	Yes	Yes	0.15
S9321 (Barlogie)	Untreated symptomatic MM, <70 years, Zubrod performance status 0-2; no cardiac or pulmonal dysfunction, no other malignancy within the last 5 years	0.05	0.07	<1%	0.03	No	No	0.55
PETHEMA (Bladé)	Newly diagnosed untreated MM, <70 years, symptomatic DSS II or III, PS 0 to 2	0.11	0.3	0.02	0.04	No	No	0.12
HOVON 24 (Sonneveld)	Untreated MM, 18-65 years, DSS II+III, no other actual or prior malignant diseases (except non-melanoma skin tumors) cardiac, pulmonary, renal or organ dysfunction, inadequate liver function, no prior radiotherapy	0.13	0.32	0.04	0.1	No	Yes	<1%
M97G (Palumbo)	Untreated MM, 50 to 70 years, abnormal cardiac, hepatic or renal function; no HBV, HCVB or HIV, no other cancer or psychiatric disease	6%	25%	0%	2%	Yes	Yes	21%
IFM 99-06 (Facon)	Untreated MM, 65-75 years or ineligible for HDT for other reasons, DSS II+III or I (high risk), no other neoplasm (except basocellular epithelioma), no amyloidosis, creatinine <50 mg/L, no cardiac or hepatic dysfunction, no infection (HIV, HepB or C)	2% (MP) 13% (MPT)	18%	2% (MP) 0% (MPT)	5%	No	No	4%

CR: Complete remission; DS: Durie-Salmon stage; EFS: event-free survival; HDT: high-dose therapy; SDT: standard-dose therapy; MM: multiple myeloma; OS: overall survival; PFS: progression-free survival; TMR: treatment related mortality.

CI=0.56-0.95). The PFS benefit with HDT was significant (p=0.018). While the same result was observed for the soubgroup analysis of 'standard protocols', HR=0.76 (95% CI=0.67-0.87), p<0.001, the analysis both of 'no TBI' and of 'long follow-up' provided no benefit in PFS for HDT, with HRs of 0.81 (95% CI=0.48-1.35), 0.81 (95% CI=0.57-1.16) respectively. Removing every single trial from the analysis reduced the PFS benefit to only a trend in two cases (p=0.055 and p=0.056), while the effect remained significant in seven cases (not illustrated). Results are illustrated in Figure 2.

Conclusion

Although myeloablative chemotherapy with stem cell support is considered standard therapy for patients younger than 65 years with no other limitations, its effect on OS for these patients remains under discussion. Therefore, Koreth *et al*. (10) undertook a systematic review to identify all RCTs that addressed that question. In their meta-analysis of nine qualified trials, they found a significant benefit in PFS but not in OS. As new data were available on two trials, we repeated the meta-analysis to further clarify the role of HDT in myeloma. With relation to all nine trials, there was no statistically significant OS benefit with HDT, which is currently still regarded as the first-line treatment. In the subgroup of 'standard protocols' we found a trend for an OS benefit with HDT. The results do still speak rather in favour of than against the actual practice guidelines as other options such as tandem or allogenic transplantation have not led to an increased OS benefit (22, 23). Whereas the introduction of novel agents has provided a large benefit for patiens with MM, it has not yet been satisfactorily evaluated whether use of novel agents is more beneficial in standard chemotherapy or in myeloablative application. Of course one problem of the interpretation of the data is the heterogeneity of the included trials, especially of the newer ones focused on patients that were only eligible for a dose-reduced myeloablative regimen. This is due to the fact that HDT has been standard therapy for many years now. Therefore, the subgroup analysis excluding these 'non-standard' trials was performed. It did not result in significantly different effects but did show a trend for improved OS for HDT. Currently conducted RCTs focus on treatment of patients with relapse (phase III: NCT00083876, www.clinicaltrials.gov) or of patients ineligible for

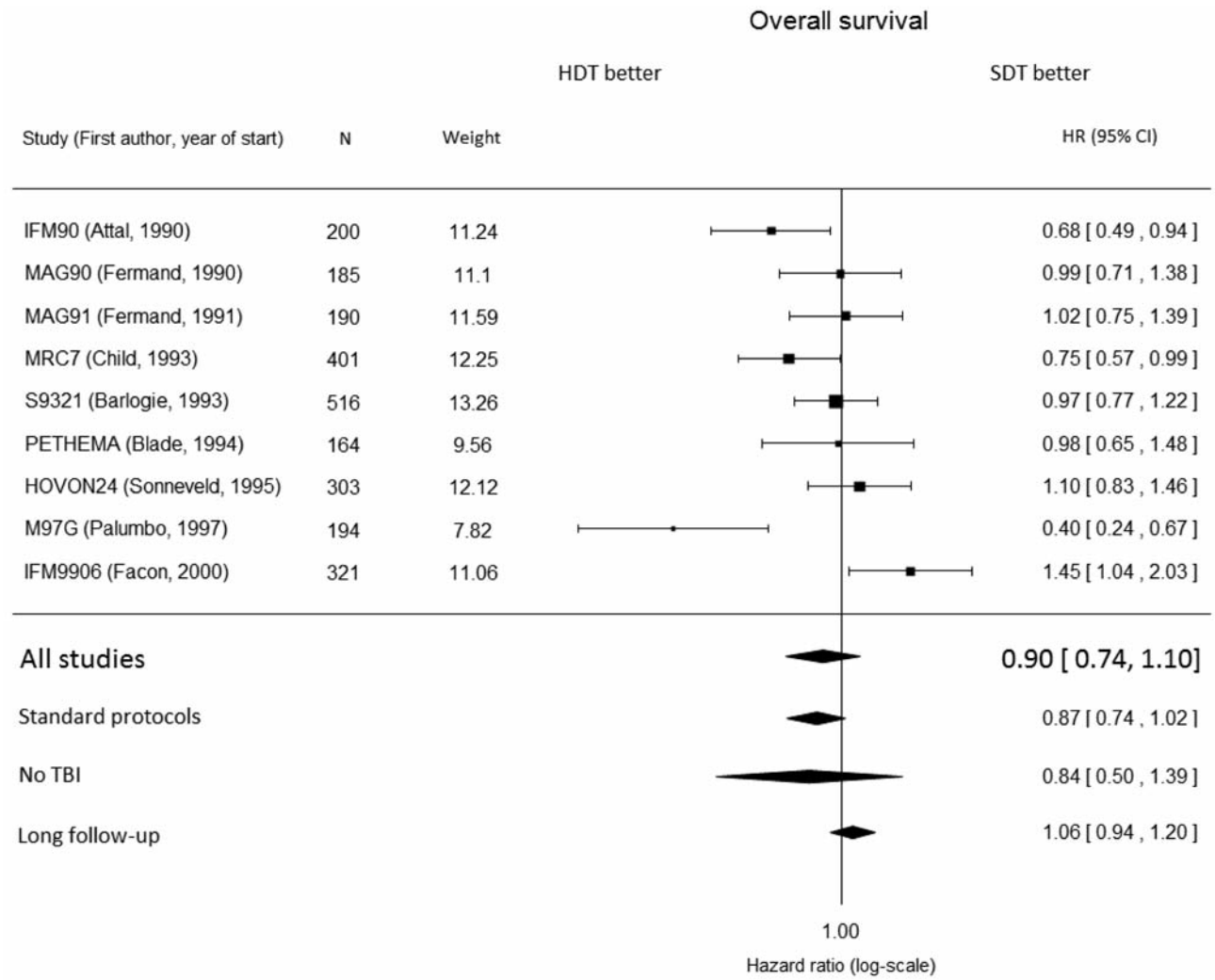

Figure 1. *Forest plot of the overall survival benefit of myeloablative chemotherapy with autologous stem cell transplantation (HDT) vs. nonmyeloablative chemotherapy (SDT). The position of a box represents the effect (confidence intervals (CI) are represented by the lines). The size of a box is proportional to the weight of the trial. Final summary effects for all studies and for subgroups are represented by diamonds. HR: Hazard ratio; N: number of participants; TBI: total body irradiation.*

conventional HDT regimens (phase III: NCT00232934, www.clinicaltrials.gov) as did some of the studies included in this meta-analysis. Additional data from ongoing clinical trials and new studies using novel agents such as thalidomide, lenalidomide and bortezomib, also in standard regimens, are warranted to finally evaluate the role of HDT in the treatment management of patients with newly diagnosed MM.

Acknowledgements

This work is part of the medical thesis of Florian Faussner and was supported by Celgene, Munich, with a travel grant for presentation at the 52nd American Society of Hematology meeting.

Support in the performance of the meta-analysis provided by Dr. Markus Pfirrmann, Institute for Medical Information Sciences, Biometry and Epidemiology, Ludwig Maximilian University Munich, is gratefully aknowledged.

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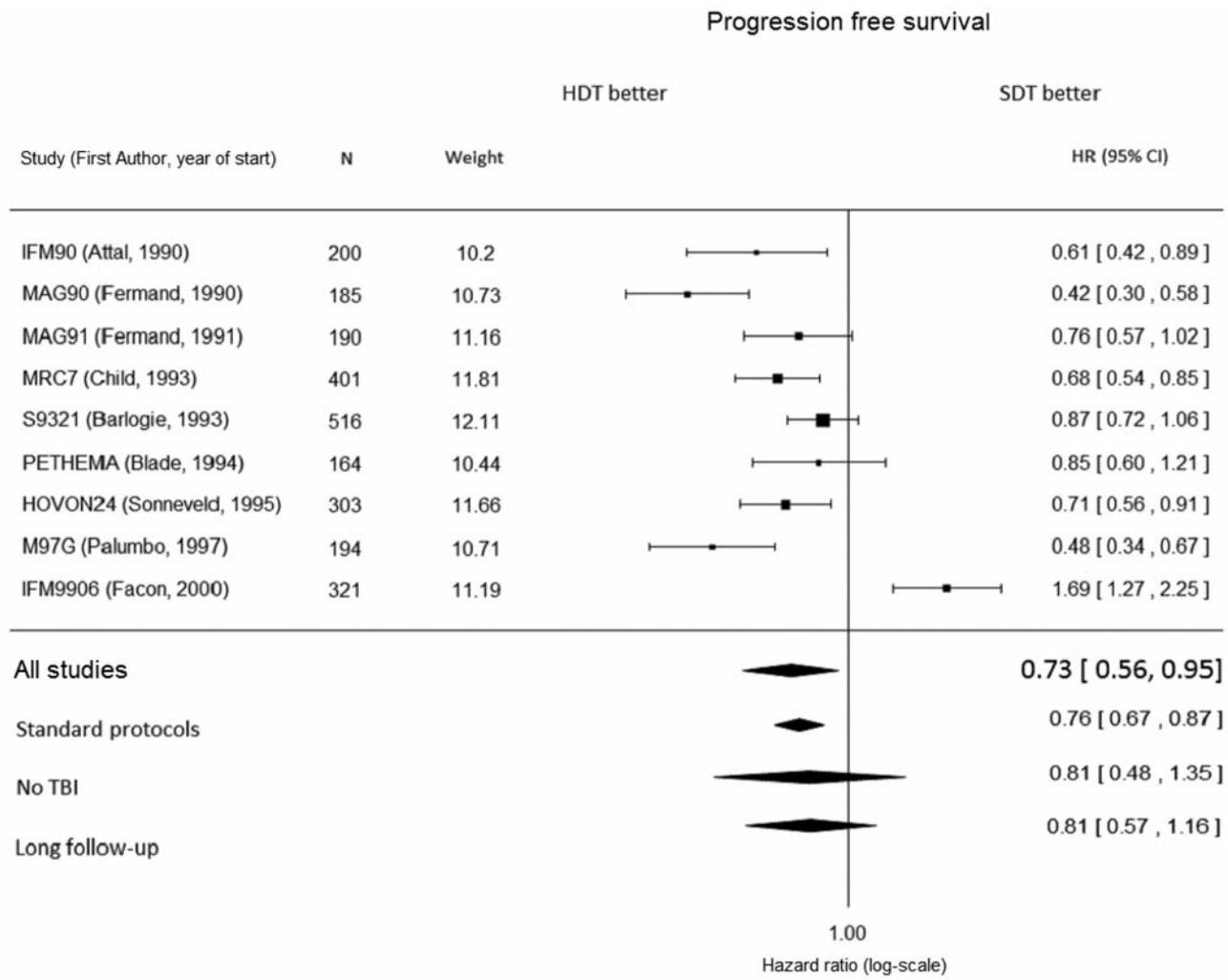

Figure 2. *Forest plot of the progression free survival benefit of myeloablative chemotherapy with autologous stem cell transplantation (HDT) vs. nonmyeloablative chemotherapy (SDT). The position of a box represents the effect (confidence intervals (CI) are represented by the lines). The size of a box is proportional to the weight of the trial. Final summary effects for all studies and for subgroups are represented by diamonds. HR: Hazard ratio; N: number of participants; TBI: total body irradiation.*

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Received June 29, 2011
Revised December 2, 2011
Accepted December 5, 2011