High-dose Therapy with Single Autologous Transplantation versus Chemotherapy for Newly Diagnosed Multiple Myeloma: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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ABSTRACT

Myeloablative high-dose therapy and single autologous stem cell transplantation (HDT) is frequently performed early in the course of multiple myeloma, supported by some randomized controlled trials (RCTs) indicating overall survival (OS) and progression-free survival (PFS) benefit compared with non-myeloablative standard-dose therapy (SDT). Other RCTs, however, suggest variable benefit. We therefore undertook a systematic review and meta-analysis of all RCTs evaluating upfront HDT versus SDT in myeloma. The primary objective was to quantify OS benefit with HDT, with PFS benefit a secondary objective. Anticipating heterogeneity, sensitivity and subgroup analyses were undertaken to assess robustness of results. Assessment of harms (treatment-related mortality) was also undertaken. We searched the PubMed, Embase, and Cochrane Collection of Controlled Trials databases using the terms *myeloma* combined with *autologous* or *transplant* or *myeloablative* or *stem cell*. In total, 3407 articles were accessed, and 10 RCTs prospectively comparing upfront HDT with SDT, with ≥2-year follow-up, and reporting OS benefit on an intent-to-treat basis were identified. Two reviewers independently extracted study characteristics, interventions, and outcomes. Hazard ratios (with 95% confidence interval) were determined. Nine studies comprising 2411 patients were fully analyzed. Significant heterogeneity was present. The combined hazard of death with HDT was 0.92 (95% confidence interval, 0.74-1.13). The combined hazard of progression with HDT was 0.75 (95% confidence interval, 0.59-0.96). The totality of the randomized data indicates PFS benefit but not OS benefit for HDT with single autologous transplantation performed early in multiple myeloma. Sensitivity and subgroup analyses supported the findings and indicated that, contrary to current reimbursement criteria, PFS benefit with upfront HDT is not restricted to chemo-responsive myeloma. However, the overall risk of developing treatment-related mortality with HDT was increased significantly (odds ratio, 3.01; 95% confidence interval, 1.64-5.50). Hence, evaluating alternative therapeutic options upfront may also be reasonable.
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KEY WORDS

Multiple myeloma • Autologous transplantation • Meta-analysis

INTRODUCTION

Upfront "high-dose" myeloablative therapy with single autologous stem cell transplantation (HDT), typically performed after a few cycles of induction therapy, is routinely recommended for most patients with newly diagnosed multiple myeloma. Treatment with HDT and single autologous transplantation is a category 1 recommendation of the National Comprehensive Cancer Network [1]; and since October 1, 2000, autologous transplantation for multiple myeloma has been a covered

procedure in the United States, per criteria of the Centers for Medicare and Medicaid Services (CMS) [2]. Myeloma is currently the leading indication for the ~4500 autologous transplantations performed annually in North America [3].

Various prospective randomized controlled trials (RCTs) [4,5], nonrandomized comparisons [6-8], and systematic reviews [9,10] have concluded that there is overall survival (OS) and progression-free survival (PFS) benefit to upfront HDT compared with nontransplantation options of "standard-dose therapy" (SDT) for de novo myeloma. However, other RCTs have indicated variable benefit to upfront HDT in myeloma [11,12]. Retrospective analyses are prone to errors of bias and confounding and may provide inaccurate estimates of effect. Prospective randomization, analyzed on an intent-to-treat basis, is a powerful means of minimizing errors. Given data from additional RCTs, prior estimates of benefit with upfront HDT need to be reassessed.

To arrive at comprehensive estimates of OS and PFS benefit from the totality of the randomized data, we undertook a systematic literature review and meta-analysis to identify all RCTs that address the utility of upfront HDT versus SDT in myeloma.

METHODS

Data Sources

We undertook 2 independent searches of the Medline (PubMed), Embase, and Cochrane Registry of Controlled Trials databases using the search term *myeloma* combined with *autologous* or *transplant* or *myeloablative* or *stem cell*. Medline (PubMed) searches were restricted to RCTs in humans, in the English language. Embase searches were restricted to articles with human subjects, in English. Cochrane database searches were not restricted by language or to human subjects. Studies identified underwent title/abstract review, and clearly nonrelevant articles were discarded. Text review of the remainder was performed to assess their suitability. The bibliographies of retained articles were examined to identify additional studies. A recent review and a meta-analysis of 3 RCTs were also accessed to identify additional studies that met inclusion criteria [3,13].

Study Selection

Studies included were prospective RCTs that evaluated upfront HDT for multiple myeloma, defined broadly as any myeloablative regimen with a single autologous transplant (or equivalent, see below), versus a comparator of upfront SDT, also defined broadly as any nontransplant option. Eligible RCTs had a minimum follow-up of 2 years and reported hazard ratios (HRs) for OS and/or PFS benefit on an intent-to-treat basis (or provided data to estimate HR (95% confidence interval [CI]) by the method of Parmar et al [14]. Unadjusted HR was used in the primary analysis of OS and PFS benefit, and adjusted HR, when available, was used in a sensitivity analysis. Odds ratio (OR) was used for treatment-related mortality (TRM) assessment. When multiple publications reported on the study, the most updated data were analyzed.

Data Extraction

Two reviewers abstracted the data independently in a standardized format. The data collected for each study included publication date, first author, year of initial patient enrollment, number randomized to each arm, patient age (years) at enrollment, duration of follow-up (months), number "at risk," and number of events for death, progression, TRM in each arm, and *P* values for OS and PFS benefit, if available. We also collected data on therapy: induction regimen and its duration, mobilization regimen, source of stem cells (bone marrow [BM] or peripheral blood [PB]), HDT and SDT regimen and duration, and maintenance therapy, if any. Discrepancies in data extraction were resolved by consensus, referring back to the original article, and contacting the study authors, if necessary.

The quality of the studies was assessed by number of participating institutions (single or multiple), method of randomization and allocation concealment (central assignment or not), dropout rate, crossover, and study power. Given the "hard" endpoints (OS and PFS) we did not assess the effect of blinding on outcomes. We did not explicitly score the methodologic quality of the included RCTs because the value of doing so is controversial. Ad hoc scores may lack demonstrated validity, and results may not be associated with quality [15-18]. Instead, we performed subgroup and sensitivity analyses and performed tests of interaction, as is widely recommended [17-19].

Data Synthesis

Data analysis was done using STATA 7 (STATA Corp, College Station, Tex). The Begg funnel plot and Egger test were used to investigate publication bias [20,21]. Heterogeneity was assessed by a Q statistic [22]. Meta-regression assessed the role of study size in heterogeneity. A Forrest plot with combined HR (95% CI) for OS and PFS benefit of upfront HDT versus SDT was constructed using the random-effects model of DerSimonian and Laird [23]. A similar plot was constructed using OR (95% CI) for TRM assessment.

We explored heterogeneity and the robustness of our findings regarding OS and PFS benefit by additional sensitivity and subgroup analyses. In sensitivity analyses of OS benefit, we assessed the effect of using
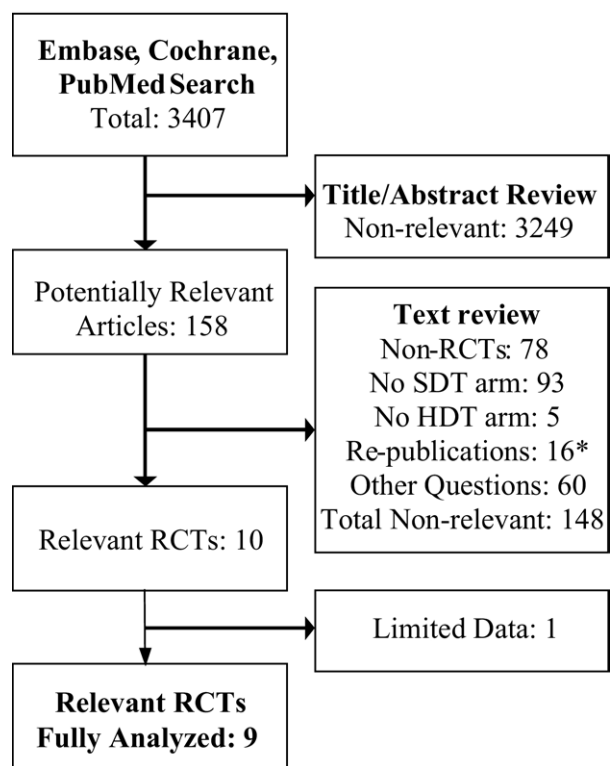
Figure 1. Search strategy flow chart. The Embase, Pubmed, and Cochrane database search and the process of identifying relevant randomized controlled trials (RCTs) for inclusion in the meta-analysis are shown. Note that the studies excluded on text review were often ineligible for multiple reasons; hence, the total number of exclusions is larger than the number of studies excluded. *One publication, a meta-analysis of 3 RCTs, provided updated hazard ratio information on overall survival benefit of high-dose therapy and single autologous stem cell transplantation (HDT) and was used in the analysis. SDT indicates nonmyeloablative standard-dose therapy.

adjusted HR, if reported by the individual studies. We also assessed the effect of including the omitted negative study (CIAM, see below) using a conservative imputed HR. In additional sensitivity analyses of OS and PFS benefit, we assessed the effect of omitting nonstandard studies and of individually removing each RCT from the analysis. In subgroup analyses, we assessed OS and PFS benefit in 3 subgroups: studies using PB stem cells (PBSCs) as a source of stem cells, studies with longer-term follow up (>48 months), and studies with lower crossover in the SDT arm.

This work was performed in accordance with the Quality of Reporting of Meta-analyses guidelines for meta-analysis of RCTs [17].

RESULTS

Systematic Review

In total, 3407 articles were identified in the initial online database searches, delineated in Figure 1. After

screening titles/abstracts, 3249 clearly nonrelevant articles were excluded (eg, nonhuman studies, nonclinical studies, reviews, addressed unrelated questions). The remaining 158 studies were retrieved. They were reviewed independently in a structured format, and studies discarded if they were non-RCTs, did not compare upfront HDT with SDT, addressed other questions, or represented the same RCT. A recent review article and a meta-analysis of 3 RCTs were also retrieved. The review article did not yield additional relevant articles [3]. The meta-analysis provided updated relative risk (HR) estimates for OS benefit with HDT for 3 RCTs [13].

The search yielded 10 unique RCTs, detailed in Tables 1-3 [4,5,11,12,24-29]. Overall, the studies were of good quality, being prospective randomized multicenter trials of adequate power, analyzed on an intent-to-treat basis, performed at the national level in the United States and Europe, and published in well-respected peer-reviewed journals (Table 2). They initiated enrollment between 1990 and 2000. Study sizes ranged from 115 to 516 randomized patients. Patients had newly diagnosed multiple myeloma, primarily Durie-Salmon stage II or III (stage I was permitted in some studies), and were typically <65 years of age (M97G and PETHEMA enrolled patients ≤70 years old and IFM9906 enrolled patients ≤75 years old; Table 3). Measurements of myeloma burden at enrollment were not consistently provided across studies. Information on treatment crossover, especially crossover of SDT to HDT on disease progression, was provided for most studies. Two groups could be determined: a higher crossover group (including MAG90 and CIAM, trials specifically designed to compare upfront versus delayed HDT) with 42%-78% SDT crossover, and a lower crossover group with 18%-23% crossover. SDT crossover information was unavailable for 2 negative studies (HOVON, IFM9906).

A nonstandard study (CIAM) randomized patients with chemoresponsive myeloma to higher-dose induction therapy (vincristine/doxorubicin/dexamethasone [VAD] and melphalan 140 mg/m^2 [MEL140]), to upfront HDT, versus no transplantation (salvage HDT was allowed) [24]. Published in abstract form, it reported no OS benefit to upfront HDT in a format precluding exact HR extraction. We imputed HR, conservatively assuming $P = .1$ (a bias favoring HDT), for a later sensitivity analysis.

The remaining 9 studies, comprising data from 2411 patients, evaluated various permutations of upfront HDT versus SDT for treatment of de novo myeloma to assess the utility of early HDT. No 2 studies had identical trial designs and therapeutic interventions, understandable particularly given the complexity of HDT, which was typically undertaken after several cycles of multiagent induction chemo-

Table 1. *Relevant Randomized Controlled Trials of Upfront HDT versus SDT for Myeloma**

Study ID	Study	Year	n	Age (y)	β2-M (mg/L)	DS III	Follow-up (mo)	HDT Regimen (Conditioning Regimen)	Stem Cell Source	SDT Regimen	Conclusion
IFM90	Attal	1990	200	58	3.5	75%	37 SDT; 41 HDT (104-OS)†	VMCP/BVAP→ (Mel140/TBI-8)	BM	VMCP/BVAP	OS: benefit; EFS: benefit
MAG90	Fermand	1990	185	48	2.8	84%	58 (104-OS)†	VAMP→ (Cc/Cy/VP/Mel140/TBI-12)	PBSC	VMCP	OS: no benefit; EFS: benefit
MAG91	Fermand	1991	190	60	3.2	81%	120	VAMP→ (Bu/Mel140 or Mel200)	PBSC	VMCP	OS: no benefit; EFS: benefit
CIAM	Facon	1992	115	52	3.5	80%	>24 (OS)	VAD/Mel140→ (Mel140/TBI-12)	BM	VAD/Mel140	OS: no benefit; PFS: NR
MRC7	Child	1993	401	55	>4	NR	31.5 SDT; 40 HDT	VAMPC→ (Mel200 or Mel140/TBI)	PBSC	ABCM	OS: benefit; PFS: benefit
S9321	Barlogie	1993	516	55	3.5	57%	76	VAD→ (Mel140/TBI-12)	PBSC	VAD-> VBMCP	OS: no benefit; PFS: no benefit
PETHEMA	Blade	1994	164	57	NR	NR	56	VBMCP/VBAD→ (Mel200 or Mel140/TBI-12)	PBSC	VBMCP/VBAD	OS: no benefit; PFS: no benefit
HOVON	Segeren	1995	261	55	3	77%	33	VAD→ Mel70x2→ (Cy60x4/TBI-9)	PBSC	VAD-> Mel70x2	OS: no benefit; EFS: no benefit
M97G	Palumbo	1997	194	64	2.9	62%	39 SDT; 41 HDT	VAD→ (Mel100x2)	PBSC	MP	OS: benefit; EFS: benefit
IFM9906	Facon	2000	248	70?	>3.5	NR	32	VAD→ (Mel100x2)	PBSC	MPT	OS: no benefit; PFS: no benefit

ABCM indicates doxorubicin, carmustine, cyclophosphamide, melphalan; β2M, β-2 microglobulin; BM, bone marrow; Bu/Mel, busulphan, melphalan; BVAP, carmustine, vincristine, doxorubicin, prednisone; Cc/Cy/VP/Mel140, lomustine, cyclophosphamide, etoposide, melphalan, XRT; Cy60, cyclophosphamide at 60 mg/kg; DS III, Durie-Salmon stage III; EFS, event-free survival; HDT, high-dose therapy and single autologous stem cell transplantation; Mel70/100/140/200, melphalan at 70/100/140/200 mg/m^2; MP, melphalan, prednisone; MPT, melphalan, prednisone, thalidomide; NR, not reported; OS, overall survival; PBSC, peripheral blood stem cell; PFS, progression-free survival; SDT, nonmyeloablative standard-dose therapy; TBI-8/9/12, total body irradiation (XRT) at 8/9/12 Gy; VAD, vincristine, doxorubicin, dexamethasone; VAMP, vincristine, doxorubicin, methylprednisolone; VAMPC, vincristine, doxorubicin, methylprednisolone, cyclophosphamide; VBAD, vincristine, carmustine, doxorubicin, dexamethasone; VBMCP, vincristine, carmustine, melphalan, cyclophosphamide, prednisone; VMCP, vincristine, melphalan, cyclophosphamide, prednisone.

*The study ID, first author, year of initial patient enrollment, study size (n, number of patients randomized), median patient age (years) at enrollment, median β2M, percentage of patients with DS III disease, and median duration of follow-up are listed. Information on HDT regimen, source of stem cells, SDT regimen, and conclusions regarding OS and PFS or EFS benefit are also shown for each study.

†Updated follow-up information (hazard ratio) on OS benefit of HDT from a repeat publication.

Table 2. *Relevant Randomized Controlled Trials of Upfront HDT versus SDT for Myeloma: Study Quality**

Study ID	Multicenter	Randomization	Assignment	Dropout after Randomization	Salvage HDT at Progression	Power
IFM90	Yes	Upfront	Central	26% (HDT)	17% (HDT)	80% for 5-y OS of 10% (SDT) vs 50% (HDT)
		Stratified: no		0% (SDT)	18% (SDT)	
MAG90	Yes	Upfront (after PBSC)	Central	2% (HDT)	NR (HDT)	80% for 20% decrease in OS rate (early vs late HDT)
		Stratified: center		0% (SDT)	78% (SDT)†	
MAG91	Yes	Upfront	Central	24% (HDT)	8% (HDT)	80% for survival benefit of HDT vs SDT, expected hazard ratio = 0.6
		Stratified: center		0% (SDT)	23% (SDT)	
CIAM	Yes?	After VAD/Mel140: chemoresponsive only	Central?	22% (HDT)	NR (HDT)	NR ("assessing survival benefit of early vs late HDT")
		Stratified: NR		NR	42% (SDT)†	
MRC7	Yes	Upfront	Central	25% (HDT)	2% (HDT)	80% for absolute 10% increased survival in HDT (target 710, actual 407)
		Stratified: age/Cr/Hb/TBI		2% (SDT)	18% (SDT)	
S9321	Yes	After VAD: all	Central	18% (HDT)	NR (HDT)	81% for 33% improved survival in HDT vs SDT
		Stratified: DS/β2M/chemoresponse		17% (SDT)	55% (SDT)	
PETHEMA	Yes	After VBMCP/VBAD: chemoresponsive only	Central	10% (HDT)	14% (HDT)	NR
		Stratified: DS		7% (SDT)	18% (SDT)	
HOVON	Yes	After VAD: all	Central?	21% (HDT)	NR (HDT)	80% for 15% better 2-y EFS after randomization in HDT (40% to 55%)
		Stratified: center		36% (SDT)	NR (SDT)	
M97G	Yes	Upfront	Central	22% (HDT)	30% (HDT)	90% for 20% increased 2-y EFS if 25% in SDT (target 240, actual 194)
		Stratified: No		4% (SDT)	48% (SDT)	
IFM9906	Yes	Upfront	Central	NR (HDT)	NR (HDT)	NR
		Stratified: center		NR (SDT)	NR (SDT)	

β2M indicates β-2 microglobulin; Cr, creatine; DS, Durie-Salmon stage; EFS, event-free survival; Hb, hemoglobin; HDT, high-dose therapy and single autologous stem cell transplantation; Mel140, melphalan at 140 mg/m²; NR, not reported; OS, overall survival; PPSC, peripheral blood stem cell; SDT, nonmyeloablative standard-dose therapy; TBI, total body irradiation; VAD, vincristine, doxorubicin, dexamethasone; VBAD, vincristine, carmustine, doxorubicin, dexamethasone; VBMCP, vincristine, carmustine, melphalan, cyclophosphamide, prednisone.

*Further information on the 10 studies listed in Table 1 is provided to better describe study quality. Information on the trial design and randomization protocol is listed. Information on dropout after randomization and crossover is provided and may be expected to reduce the differences between the 2 arms. Information on study statistical power calculations a priori is also provided. Areas of uncertainty (?) are indicated.

†Per protocol, salvage HDT was undertaken upon disease progression.

Table 3. *Relevant Randomized Controlled Trials of Upfront HDT versus SDT for Myeloma: Entry Criteria, Toxicity, Response, and Maintenance Therapy**

Study ID	Entry Criteria	TRM		CR		Maintenance	
		SDT	HDT	SDT	HDT	SDT	HDT
IFM90	Untreated MM DS II/III; age <65 y; LVEF/DLCO >50%; adequate hepatic function; no other cancer or psychiatric disease	5.0%	7.0%	5%††	22%††	IFN	IFN
MAG90	Untreated symptomatic MM DS II/III (1 course of steroids and/or local XRT not precluding TBI was allowed); age <56 y; adequate cardiac, pulmonary, hepatic, and renal functions	0%†	12.1†	5%	19%	IFN	IFN
MAG91	Untreated symptomatic MM DS II/III (1 course of steroids and/or local XRT not precluding TBI was allowed); age 55-65 y; adequate cardiac, pulmonary, hepatic, and renal functions	2.1%‡	5.3%‡	4%	6%	IFN	IFN
CIAM	Untreated MM DS II/III; age <60 y	1.8%	5.0%	18%	32%	IFN	IFN
MRC7	Untreated MM; met MRC criteria for treatment; age <65 y; suitable candidate for HDT	NR¶	3.0%§	8%	44%	IFN	IFN
S9321	Untreated symptomatic MM; age ≤70 y; PS 0-2#; LVEF/DLCO ≥50%; no prior malignancy (except nonmelanoma skin tumor or cervical carcinoma in situ) in past 5 y	0.4%	3.4%	11%	11%	IFN vs none§§	IFN vs none§§
PETHEMA	Newly diagnosed untreated symptomatic MM DS II/III; age <65 y‡‡; PS 0-2	3.6%	3.7%	11%	30%	IFN+Dex	IFN+Dex
HOVON	Untreated MM DS II/III A/B; PS <4**; adequate pulmonary, cardiac, neurologic, metabolic, and hepatic functions; no prior extensive XRT or malignant disease (except nonmelanoma skin tumor or stage 0 cervical carcinoma)	1.3%	5.2%‖	13%	29%	IFN	IFN
M97G	Untreated MM; age 50-70 y; LVEF/DLCO ≥50%; adequate hepatic, renal function; no hepatitis B or C or HIV; no cancer or psychiatric disease	0%	2.1%	6%††	25%††	IFN+Dex	IFN+Dex
IFM9906	MM; age 65-75 y	0%	4.0%	16%	17%	—	—

CR indicates complete remission; DLCO, diffusing capacity of the lung for carbon monoxide; HDT, high-dose therapy and single autologous stem cell transplantation; HIV, human immunodeficiency virus; IFN, interferon; IFN+Dex, interferon plus dexamethasone; LVEF, left ventricular ejection fraction; MM, multiple myeloma; nCR, near complete remission; NR, not reported; PS, performance status score; SDT, nonmyeloablative standard-dose therapy; TBI, total body irradiation; TRM, transplant-related mortality; XRT, radiation therapy.

*Additional information on the trial entry criteria, TRM and CR rates, and maintenance therapy on the 10 studies listed in Table 1 is provided, when available from the original publications. The TRM data in particular were variably reported and had to be inferred for some studies, as indicated.

†TRM at 1 year; in the SDT arm, TRM after salvage HDT was 14%.

‡TRM at 6 months; in the HDT arm, 1 of 71 patients who actually underwent stem cell transplantation had a toxic death.

§TRM at 100 days after stem cell transplantation.

‖TRM within 3 months after myeloablative therapy was 3.9%.

¶Imputed as 0 for calculating odds ratio.

#Zubrod PS; PS 3-4 as a result of myeloma related bone disease was permitted.

**World Health Organization PS.

††Including nCR. In IFM90, CR was not confirmed by immunofixation in all cases. CR was not a category for M97G (only nCR used).

‡‡From 1997 the upper age limit was extended to 70 years.

§§Chemoresponders were randomized to IFN versus observation.

therapy. HDT comprised autologous stem cell collection from PB or BM (with or without growth factors and/or chemotherapy) followed by myeloablative conditioning chemotherapy (with or without radiation) and subsequent autologous stem cell infusion (with or without growth factor support). The patients were randomized upfront or after induction therapy. Several RCTs used additional nonstandard approaches, as discussed below. These were included in the initial analysis and removed in a sensitivity analysis.

In a nonstandard study evaluating patients 50-70 years of age (M97G), the HDT arm received multiagent induction therapy (VAD) followed by tandem autologous transplants, each after "intermediate-dose" melphalan conditioning (MEL100) [27]. The total conditioning dose (MEL100x2) was considered possibly similar to that used for single autologous transplantation (MEL200); hence, the study was included in the initial analysis. Tandem transplantation in the HDT arm, lower intensity chemotherapy (melphalan-prednisone) for the SDT arm, and lack of equivalent induction therapy in the SDT arm were nonstandard.

A similar nonstandard study (IFM9906), a recent plenary presentation at the 2006 annual meeting of the American Society of Clinical Oncology, evaluated patients 65-75 years of age by comparing HDT comprising multiagent induction therapy (VAD) followed by tandem autologous transplants, each after intermediate-dose MEL100 conditioning, with SDT comprising melphalan/prednisone/thalidomide chemotherapy only [29]. Considering the total conditioning dose (MEL100x2) as possibly comparable to the MEL200 used in other studies, this study was included in the initial analysis. The elderly study population, tandem intermediate-dose transplants in the HDT arm, and lack of equivalent induction therapy in the SDT arm were nonstandard.

Another nonstandard study (HOVON) used more intensive induction chemotherapy (VAD plus MEL70x2) for all, adding myeloablative conditioning (cyclophosphamide) and autologous transplantation in the HDT arm [26]. The higher doses of chemotherapy, occasionally necessitating stem cell rescue in the SDT arm, were considered nonstandard.

In the fourth study (MAG90), subjects in the SDT arm were permitted salvage HDT, per protocol, for disease relapse or progression, a nonstandard approach [25]. This study design was acceptable for inclusion in the initial analysis because a proportion of patients randomized to the SDT arm in other studies also went on to receive rescue HDT upon disease progression.

A fifth study (PETHEMA) provided upfront induction therapy (VAD), randomizing only chemoresponsive patients to HDT versus SDT, arguably a nonstandard approach [11]. This was acceptable for inclusion in the initial analysis because most patients

in the other studies had chemoresponsive disease, indicating substantial overlap in patient populations.

Publication Bias

We constructed funnel plots to evaluate for publication bias. The Begg funnel plot for OS benefit had a relatively symmetric distribution, arguing against publication bias (Begg test, $P = .92$; Egger test, $P = .91$). Similarly, the funnel plot for PFS benefit showed no evidence for publication bias visually or statistically (Begg test, $P = .47$; Egger test, $P = .95$).

HDT and OS Benefit

All studies reported OS as the primary endpoint. The summary hazard estimates vary between studies, ranging from 0.40 (HDT better) to 1.70 (SDT better). There was significant heterogeneity in the estimates across studies, with a Q statistic of 27.65 ($P < 0.01$; 8 df). Meta-regression indicated no role for study size in heterogeneity ($P = .87$).

A Forrest plot of the individual and combined HRs (95% CI) for OS benefit with upfront HDT is shown in Figure 2. The combined HR for OS benefit was 0.92 (95% CI, 0.74-1.13) for the 9 studies. The overall estimate does not indicate a statistically significant reduction in hazard of death with upfront HDT for newly diagnosed myeloma ($P = .40$).

We explored the robustness of the results with sensitivity analyses, summarized in Figure 2. Using adjusted HR, when available, for OS benefit indicated a combined HR of 0.92 (95% CI, 0.75-1.13). For the negative CIAM study, a conservative bias in favor of HDT yielded an unlikely study HR of 0.51 (95% CI, 0.23-1.14), given the known study OR of 0.90 (95% CI, 0.36-2.20), yet resulted in an overall HR of 0.89 (95% CI, 0.73-1.09) for all 10 studies. Of the original 9 RCTs, upon removing the 2 nonstandard tandem intermediate-dose studies (M97G, IFM9906), combined HR for OS benefit for the remaining 7 studies was 0.91 (95% CI, 0.80-1.04). Similarly, upon excluding all nonstandard studies (M97G, HOVON, MAG90, PETHEMA, IFM9906), combined HR of OS benefit for the remaining 4 studies was 0.85 (95% CI, 0.71-1.03). Removing any single study from the analysis did not reduce the combined 95% CI below 1.00 (data not shown).

In a subgroup analysis, OS benefit for the 8 studies preferentially using PBSCs as a stem cell source indicated a combined HR of 0.95 (95% CI, 0.76-1.19). Similarly, OS benefit for the 5 studies with longer follow-up (>48 months) yielded a combined HR of 0.92 (95% CI, 0.80-1.06). OS benefit for studies with lower crossover in the SDT arm indicated a combined HR of 0.83 (95% CI, 0.69-1.01), despite excluding 2 negative studies with missing crossover information
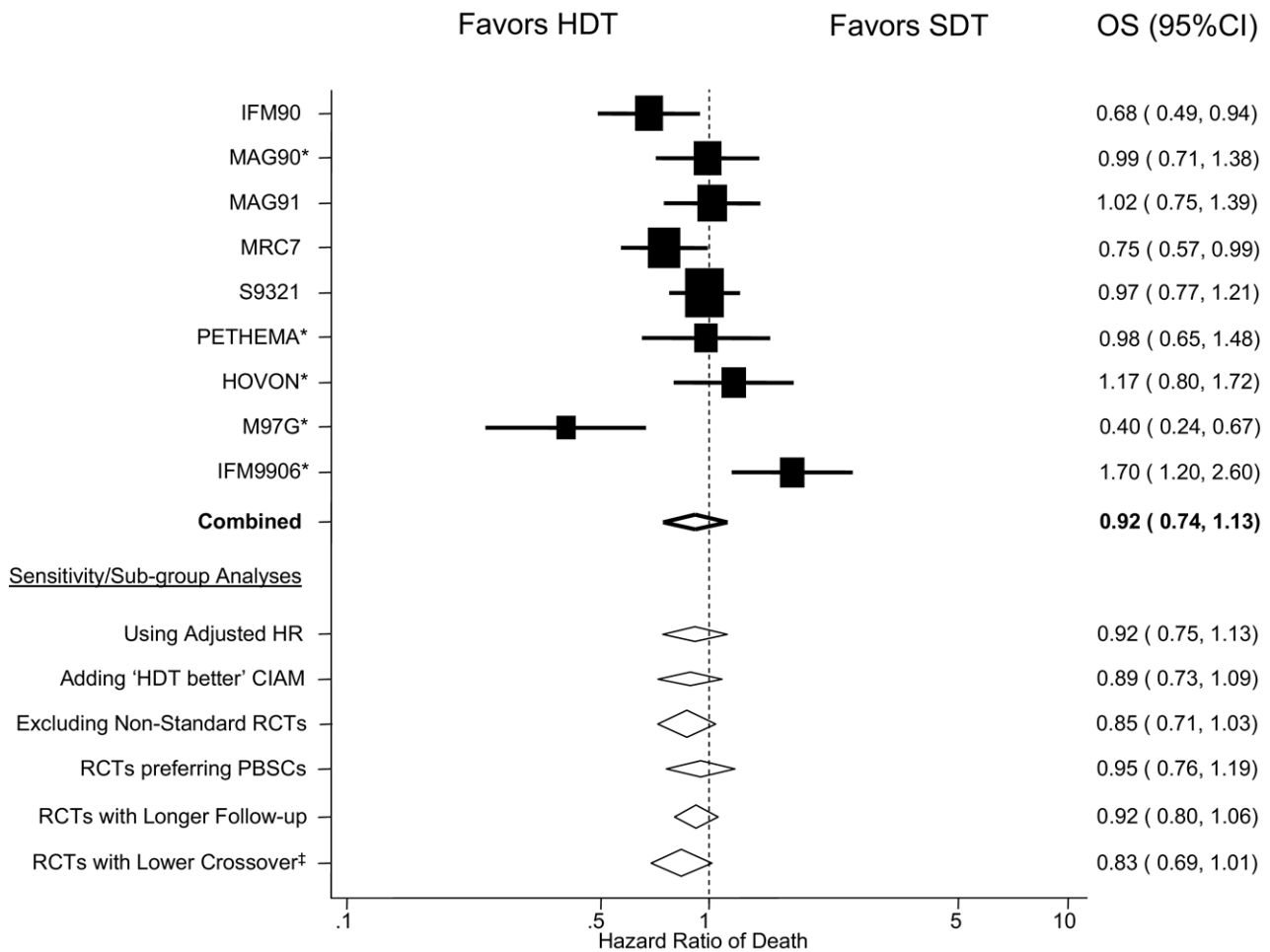
Figure 2. Forrest plot of overall survival (OS) benefit of upfront high-dose therapy and single autologous stem cell transplantation (HDT) in myeloma. The individual randomized controlled trials (RCTs) are indicated on the y axis. The summary effect estimate (hazard ratio [HR]) for individual RCTs are indicated by black rectangles (the size of the rectangle is proportional to the study weight), with the lines representing 95% confidence intervals (CIs). The overall summary effect estimate (HR) and 95% CI are indicated by the diamond below. Overall estimates after sensitivity and subgroup analyses are shown below. The corresponding values for HR (95% CI) are indicated alongside. *Nonstandard study. ‡ Two negative studies (HOVON, IFM9906) with missing crossover information were omitted from this analysis. PBSC indicates peripheral blood stem cell; SDT, nonmyeloablative standard-dose therapy.

(HOVON, IFM9906). Tests of interaction for secondary analyses were nonsignificant.

HDT and PFS

No estimate of PFS benefit was available for the CIAM study. The remaining 9 studies reported on myeloma-free survival. This outcome was defined variably as event-free survival or PFS. Both terms have been grouped together as PFS for this analysis because they are similarly defined as time from randomization to death, progression, or relapse, censored at last known follow-up. HR for PFS benefit ranged from 0.42 (HDT better) to 1.80 (SDT better). Significant heterogeneity was present between studies, with a Q statistic of 51.57 ($P < .01$; 8 df). Meta-regression did not detect a significant role for study size in heterogeneity ($P = .56$).

The Forrest plot with individual and combined

HRs (95% CI) for PFS benefit with HDT is shown in Figure 3. The combined HR for the 9 studies was 0.75 (95% CI, 0.59-0.96), indicating statistically significant PFS benefit with upfront HDT ($P = .02$). We explored the robustness of the result with sensitivity analyses, summarized in Figure 3. Removal of the 2 tandem intermediate-dose studies (M97G, IFM9906) indicated a combined HR for PFS benefit of 0.71 (95% CI, 0.59-0.85) for the remaining 7 studies. Further, removal of all nonstandard studies (MAG90, M97G, HOVON, PETHEMA, IFM9906) yielded a PFS benefit combined HR of 0.75 (95% CI, 0.65-0.87) for the 4 remaining studies. Individually removing any study from the combined analysis did not widen the 95% CI above 1.00 (data not shown).

On subgroup analysis (Figure 3), the PFS benefit in 8 studies using PBSCs preferentially as a stem cell source yielded a combined HR estimate of 0.77 (95%
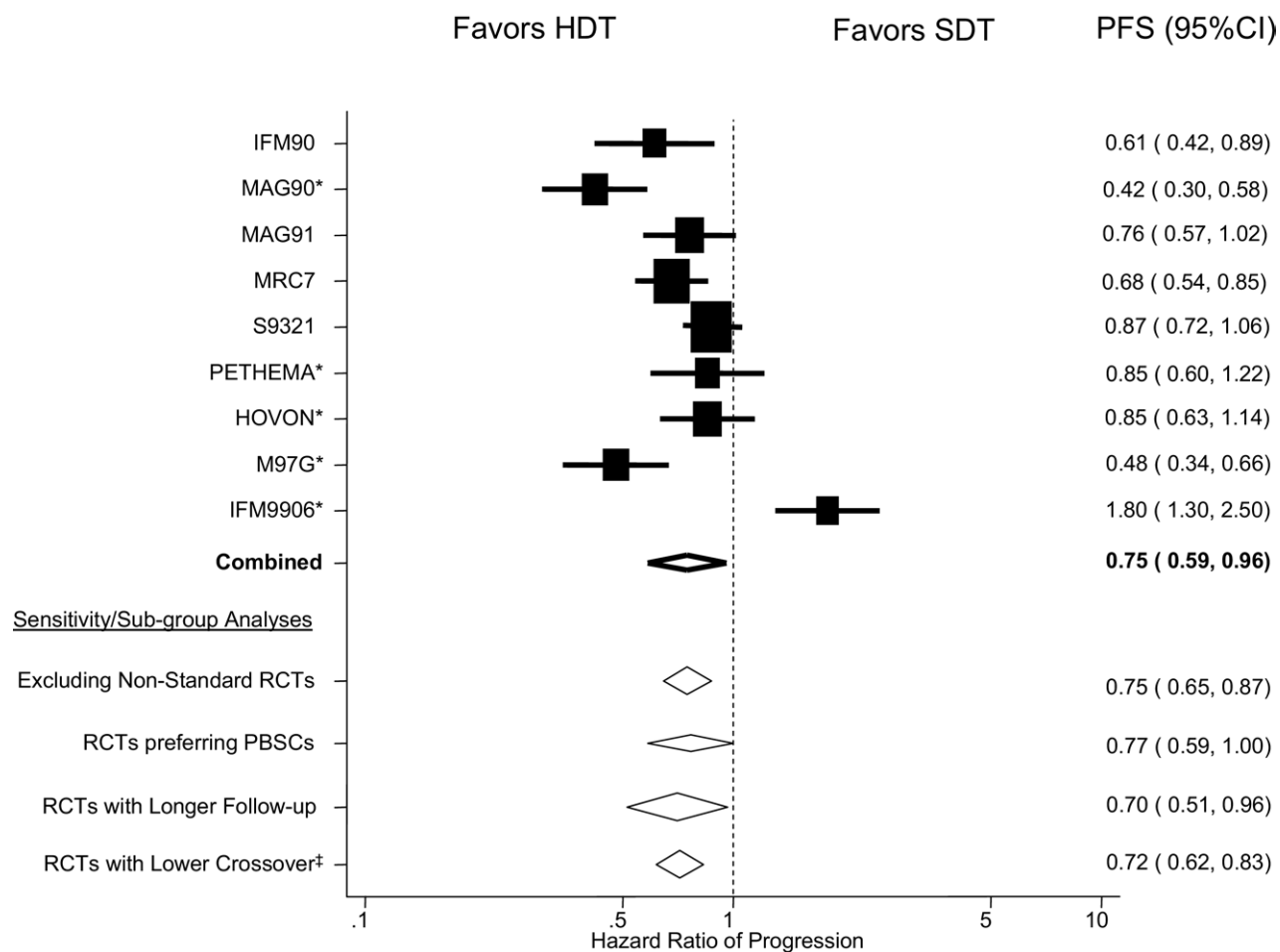
Figure 3. Forrest plot of progression-free survival (PFS) benefit of upfront high-dose therapy and single autologous stem cell transplantation (HDT) in myeloma. The individual randomized controlled trials (RCTs) are indicated on the y axis. The summary effect estimate (hazard ration [HR]) for individual RCTs are indicated by black rectangles (the size of the rectangle is proportional to the study weight), with lines representing 95% confidence intervals (CIs). The overall summary effect estimate (HR) and 95% CI are indicated by the diamond. Overall estimates after additional sensitivity and subgroup analyses are shown below. The corresponding values for HR (95% CI) are indicated alongside. * Nonstandard study. ‡ Two negative studies (HOVON, IFM9906) with missing crossover information were omitted from this analysis. PBSC indicates peripheral blood stem cell; SDT, nonmyeloablative standard-dose therapy.

CI, 0.59-1.00). The 4 studies with longer follow-up (>48 months) had a combined HR estimate of 0.70 (95% CI, 0.51-0.96). After omitting 2 negative studies (HOVON, IFM9906) with missing crossover information, the 4 studies with lower SDT crossover had a combined HR estimate of 0.72 (95% CI, 0.62-0.83). Tests of interaction for secondary analyses were nonsignificant.

HDT and TRM

Information on toxic deaths was reported directly or indirectly (eg, as percentage) for most studies (Table 3). However, information on the denominator (number at risk) was variably reported, if at all. Hence, in the interests of uniformity, all patients enrolled on an intention-to-treat basis were included in the denominator across studies. Because this may underestimate the actual toxicity of undergoing therapy, it is a

bias favoring the more toxic treatment (HDT). The Forrest plot with individual and combined OR for TRM risk with HDT is shown in Figure 4. The combined OR for the 9 studies was 3.01 (95% CI, 1.64-5.50), indicating significantly increased TRM with upfront HDT (*P* < .01).

DISCUSSION

Early autologous transplantation for myeloma is common, based on observational and RCT data indicating significant OS benefit for HDT performed after a few cycles of multiagent induction chemotherapy. Child et al [5], presenting their study findings, combined OR estimates from 3 RCTs to demonstrate statistically significant OS benefit to upfront HDT. Subsequently, RCTs addressing the same overall question, but differing with regard to specifics of pa-
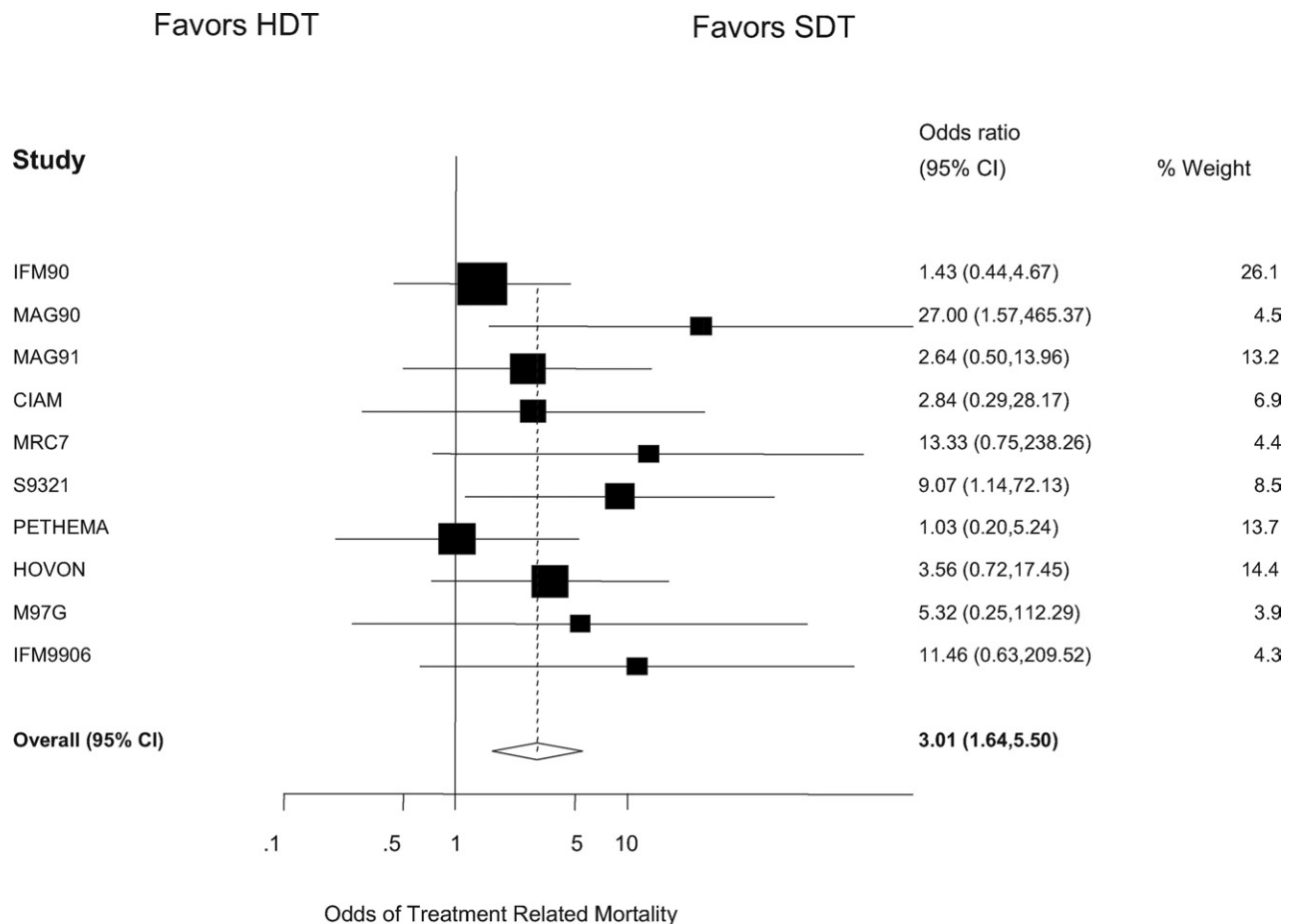
Figure 4. Forrest plot of treatment-related mortality risk of upfront high-dose therapy and single autologous stem cell transplantation (HDT) in myeloma. The individual randomized controlled trials (RCTs) are indicated on the y axis. The summary effect estimate (odds ratio) for individual RCTs are indicated by black rectangles (the size of the rectangle is proportional to the study weight), with lines representing 95% confidence intervals (CIs). The overall summary effect estimate (odds ratio) and 95% CI are indicated by the diamond. SDT indicates nonmyeloablative standard-dose therapy.

tient eligibility, population randomized, specifics of HDT and SDT, and other study factors, have reached different conclusions regarding the utility of such up-front HDT. However, the effect, if any, of this additional information is unclear, and treatment of myeloma remains the leading indication for autologous transplantation in North America.

In part this may be because all the RCT data have not yet been systematically assessed. In this regard, heterogeneity arising from structural and methodologic differences between studies may be a factor, despite their similar overall focus on evaluating the utility of upfront HDT versus nontransplantation therapeutic options in myeloma. However, failing to systematically assess the available data is suboptimal, resulting in a relatively arbitrary preferment of individual study results or an "intuitive" data synthesis, without objective means to test the robustness of any conclusions. Instead, quantitatively integrating the total RCT data available will likely enhance our understanding of the role of

HDT in newly diagnosed myeloma. The robustness of any conclusions can then be systematically assessed in secondary analyses.

It is possible that the favorable early RCT results were simply the play of chance. For instance, the first trial comparing HDT with SDT reported an absolute OS benefit of 40%, an improvement rarely sustained in oncology [4]. A subgroup comparison of the 3 RCTs reported by Child et al [5] with the subsequent trials yielded a nonsignificant test of interaction (data not shown) and supports our evaluating the RCT data in its entirety. Promising early results can lead to "optimism bias" with subsequent rapid adoption of new technologies [30].

To comprehensively assess the utility of early myeloablative therapy with single autologous transplantation in myeloma, we defined HDT and SDT broadly to identify all relevant RCTs evaluating upfront transplant versus nontransplant modalities and used the random effects model to quantify overall benefit. We also identified nonstandard studies a pri-

ori (to guard against "cherry picking") and assessed their effect on the results.

The systematic literature search identified 10 prospective RCTs comparing upfront HDT with SDT for newly diagnosed multiple myeloma, 3 of which (IFM90, MRC7, and M97G) reported OS benefit to upfront HDT (Table 1). Initiated between 1990 and 2000, the studies are relatively mature. They varied in the specific therapies used (Table 1). For the HDT arm, myeloablative conditioning commonly comprised 200 mg/m^2 melphalan (MEL200) or 140 mg/m^2 melphalan plus 8- to 12-Gy total body irradiation (TBI). PBSCs were the preferred stem cell source in all except 2 studies (IFM90, CIAM). One negative study (CIAM) provided limited information on OS benefit and could not be included in the initial analysis (but was used in a sensitivity analysis). Nine studies were systematically assessed to obtain a combined HR (95% CI) for OS and PFS benefit. Five of these studies (MAG-90, M97G, HOVON, PETHEMA, and IFM9906) were considered nonstandard. They were included in the initial analysis and removed in a sensitivity analysis.

As anticipated, despite their similar overall focus on the utility of upfront HDT for myeloma, structural differences between studies likely resulted in the significant heterogeneity observed across studies. Differences in study size, duration of follow-up, or stem cell source did not explain the heterogeneity observed. Because we depended on data extractable from the original publications, we could not assess the role of other patient or disease variables (eg, performance status, serum creatinine, β-2 microglobulin, disease stage, cytogenetics) in explaining heterogeneity.

Our primary finding is that the totality of the randomized data indicate no statistically significant OS benefit to upfront HDT in newly diagnosed myeloma ($P = .40$). The lack of OS benefit was evident despite our inability to include a relevant negative study (CIAM). This conclusion was supported by various sensitivity and subgroup analyses. The finding was not dependent on an individual study because removal of any single study did not change the conclusion. Similarly, excluding nonstandard studies did not affect the overall conclusion. Lack of longer-term follow-up is also unlikely to explain the negative findings because the studies are relatively mature, being initiated in the previous decade. Further, the studies reporting significant OS benefit did not have appreciably longer follow-up than the negative studies, and the subgroup of studies with longer follow-up (>48 months) also showed no OS benefit. A secondary finding is of statistically significant PFS benefit with upfront HDT ($P = .02$). The PFS benefit was stable on sensitivity and subgroup analyses.

Would improved HDT methodologies result in improved OS benefit? Owing to faster engraftment and lower anticipated toxicity, PBSCs are preferred to BM as a stem cell source for autologous transplantation [10]. Interestingly, overall results from the 8 RCTs preferentially using PBSCs did not indicate greater OS benefit. Similarly, for HDT, myeloablative conditioning with MEL200 is considered less toxic and preferable to MEL140/TBI [31]. Most studies analyzed permitted MEL200 or MEL140/TBI conditioning in the HDT arm and did not report outcomes separately on this basis. We therefore cannot comment on the effect of MEL200 conditioning directly, but have listed the TRM for each study, if available, in Table 3. In addition, maintenance therapy, typically with interferon, was typically used for the HDT and SDT arms in these studies. However, the single study addressing the role of maintenance therapy (S9321) randomized responsive patients in both arms to interferon versus observation and found no OS or PFS benefit with maintenance interferon.

There does not appear to be any simple concordance between these methodologic factors and outcome. For instance, the IFM90 study, despite using MEL140/TBI conditioning and BM stem cells in the HDT arm, reported highly significant OS benefit for upfront HDT. It is therefore less likely that lack of PBSCs or MEL200 in the HDT arm significantly accounts for the lack of overall OS benefit. Interestingly, dexamethasone, a highly active agent in myeloma, was not used in 2 of the studies indicating OS benefit to upfront HDT (IFM90, MRC7). It is a matter of speculation as to whether using more active agents for induction or maintenance would have improved outcomes in the SDT arms.

What about the role of treatment crossover? A significant fraction of patients randomized to SDT ultimately received salvage HDT on or off protocol (Table 2). The 2 studies (MAG90, CIAM) directly evaluating "early" (upfront) HDT versus "delayed" HDT (no upfront transplantation, with provision for rescue HDT, ie, crossover) independently concluded that there was no OS benefit to upfront HDT. Such crossover, analyzed on an intent-to-treat basis, is anticipated to reduce observable differences in outcome. Importantly however, crossover of patients on the SDT arm occurred primarily upon disease progression or relapse, and a priori, salvage HDT performed later in the disease course was not anticipated to be equivalent to upfront HDT. In addition, studies in the lower crossover group showed no overall OS benefit to upfront HDT, despite excluding 2 negative studies (HOVON, IFM9906) lacking crossover information.

What is the role of early HDT in chemoresponsive myeloma? CMS criteria specifically mandate chemoresponsive disease (with at least a partial response to induction therapy) to be eligible for upfront HDT [2]. However, the 2 RCTs evaluating HDT in this

setting (CIAM, PETHEMA) concluded there was no OS benefit. The randomized OS data therefore do not support the CMS requirement. However, chemotherapy responsiveness was defined broadly in studies, whereas it may be reasonable to consider the minority of patients with a complete response distinct from those with a partial response. Nevertheless, evidentiary basis for this reimbursement criterion is unclear. Given its emphasis on linking evidence-based decision making to reimbursement, our analysis has immediate practical implications for CMS: approval criteria for autologous transplantation in myeloma should be revised to remove this restriction. If transplantation is considered beneficial for patients with chemoresponsive disease on the basis of PFS benefit, it is equivalently so for all patients with newly diagnosed myeloma.

We caution that a finding of a lack of significant OS benefit with upfront HDT cannot be interpreted as arguing against any role for autologous transplantation in myeloma. A significant PFS benefit alone may constitute sufficient justification for upfront HDT, particularly if a quality-of-life benefit can be demonstrated. It is also possible that certain patient subgroups (eg, poor-risk cytogenetics) may obtain benefit significantly different from the overall estimates we derived. However, it is also important to consider the harms associated with upfront HDT, particularly given the documented lack of OS benefit. Our TRM analysis indicates that the overall odds of death due to treatment toxicity are significantly increased with upfront HDT (OR, 3.01; 95% CI, 1.64-5.05). Given an event rate of 2.0 % in the SDT arm (weighted SDT average across studies), 1 excess toxic death per ~26 patients enrolled may be anticipated with upfront HDT compared with SDT (Table 4). The dilemma with upfront HDT is thus between increased short-term risks (TRM) and long-term PFS benefit.

There are limitations to our analysis. As a meta-analysis of the published literature, we extracted summary risk statistics (HR) from individual studies to determine combined risk estimates. Dependence on published articles limit the level of detail that can be captured regarding subgroups that may have greater or lesser benefit from the intervention, an area of particular interest. A meta-analysis of updated individual patient data from all 10 RCTs is an optimal way to determine more complete estimates of OS and PFS benefit with HDT and to assess additional outcomes such as effect on quality of life (eg, TWiST, Time without Symptoms or Toxicity). The proposed meta-analysis could also assess additional patient, disease, or treatment covariates that affect outcomes of interest (eg, cytogenetics). Nonetheless, our quantitative analysis of published data from 9 RCTs comprising 2411 prospectively randomized patients provides the most

Table 4. *Assessment of Potential Harm (TRM) with Upfront HDT**

TRM Event Rate		Number Needed for Treatment Harm (HDT)†	Number of Excess Events (Toxic Deaths)/1000†
SDT Group	HDT Group†		
0.005	0.015	101.0	9.9
0.010	0.030	51.3	19.5
0.015	0.044	34.7	28.8
0.020	0.058	26.4	37.9
0.025	0.072	21.4	46.6
0.030	0.085	18.1	55.2

HDT indicates high-dose therapy and single autologous stem cell transplantation; SDT, nonmyeloablative standard-dose therapy; TRM, transplant-related mortality.

*Table presents the anticipated TRM with upfront HDT (based on 3-fold increased odds of death with HDT versus SDT), for a range of possible TRM rates in the SDT arm. Based on these estimates, the number of patients that need to be enrolled to the HDT arm to have 1 excess HDT toxicity-related death (versus those in the SDT arm) is also indicated, as is the number of such excess deaths anticipated per 1000 patients enrolled to upfront HDT.

†Based on an odds ratio of 3.010 applied to the control group (SDT) event rate.

complete estimate of treatment effect available. It forms the basis for an informed assessment of the benefits of upfront HDT in newly diagnosed multiple myeloma.

If upfront HDT using single autologous transplantation does not offer a significant OS benefit, how should we treat newly diagnosed myeloma? A priori, 2 alternative approaches appear attractive. One approach, using more intensive therapy with upfront tandem autologous stem cell transplantation (HDT × 2), has randomized data supporting its use, and additional studies are underway [32,33]. Similarly, evaluation of intensive therapy with nonmyeloablative allogeneic transplantation is ongoing [34,35].

Conversely, newer myeloma-specific therapies (eg, thalidomide, bortezomib, lenalidomide) offering enhanced response rates are available [36-38]. In this regard, it is interesting that the IFM9906 study, showing OS and PFS benefits to SDT, added thalidomide to the standard melphalan-prednisone chemotherapy arm. Increasingly used for induction therapy before transplantation and for maintenance therapy after transplantation, such agents may also improve the efficacy of HDT. It will be important to prospectively evaluate the benefit of early versus delayed HDT in the context of such novel agents, to better define their role in the treatment of de novo myeloma.

Choosing between these different options is not straightforward. Many would consider a PFS benefit sufficient basis for upfront HDT in patients with newly diagnosed myeloma. Whether this argument is persuasive given the availability of newer antimyeloma therapies and whether benefit is equivalent for all clinically relevant subgroups is unclear. Decisions re-

garding the role and timing of HDT will need to be made in collaboration with our patients, acknowledging uncertainty, and incorporating their preferences. Enrollment in clinical trials that seek to address such issues is to be encouraged.

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REFERENCES

1. Anderson KC, Alsina M, Bensinger W, et al. *NCCN Clinical Practice Guidelines in Oncology v1.2006-Multiple Myeloma*; 2006. Available at: http://www.nccn.org/professionals/physician_gls/PDF/myeloma.pdf. Accessed July 7, 2006.

2. Centers for Medicare and Medicaid Services. *Medicare National Coverage Determinations Manual*. Section 110.8.1v4:16; 006. Available at: http://www.cms.hhs.gov/mcd/viewncd.asp?ncd_id=110.8.1&ncd_version=4&basket=ncd%3A110%2E8%3A4%3AStem+Cell+Transplantation. Accessed July 7, 2006

3. Hari P, Pasquini MC, Vesole DH. Cure of multiple myeloma—more hype, less reality. *Bone Marrow Transplant*. 2006;37:1-18.

4. Attal M, Harousseau JL, Stoppa AM, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. *N Engl J Med*. 1996;335:91-97.

5. Child JA, Morgan GJ, Davies FE, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. *N Engl J Med*. 2003;348:1875-1883.

6. Lenhoff S, Hjorth M, Holmberg E, 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.

7. Palumbo A, Triolo S, Argentino C, et al. Dose-intensive melphalan with stem cell support (MEL100) is superior to standard treatment in elderly myeloma patients. *Blood*. 1999;94:1248-1253.

8. Gianni AM, Tarella C, Bregni M, et al. High-dose sequential chemoradiotherapy, a widely applicable regimen, confers survival benefit to patients with high-risk multiple myeloma. *J Clin Oncol*. 1994;12:503-509.

9. Imrie K, Esmail R, Meyer RM. The role of high-dose chemotherapy and stem-cell transplantation in patients with multiple myeloma: a practice guideline of the Cancer Care Ontario Practice Guidelines Initiative. *Ann Intern Med*. 2002;136:619-629.

10. Hahn T, Wingard JR, Anderson KC, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of multiple myeloma: an evidence-based review. *Biol Blood Marrow Transplant*. 2003;9:4-37.

11. Blade J, Rosinol L, Sureda A, 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;106:3755-3759.

12. Fermand JP, Katsahian S, Divine 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 Myeloma-Autogreffe. *J Clin Oncol*. 2005;23:9227-9233.

13. Levy V, Katsahian S, Fermand JP, Mary JY, Chevret S. A meta-analysis on data from 575 patients with multiple myeloma randomly assigned to either high-dose therapy or conventional therapy. *Medicine*. 2005;84:250-260.

14. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Stat Med*. 1998;17:2815-2834.

15. Greenland S. Invited commentary: a critical look at some popular meta-analytic methods. *Am J Epidemiol*. 1994;140:290-296.

16. Juni P, Witschi A, Bloch R, Egger M. The hazards of scoring the quality of clinical trials for meta-analysis. *JAMA*. 1999;282:1054-1060.

17. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. *Lancet*. 1999;354:1896-1900.

18. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000;283:2008-2012.

19. Hasselblad V, Eddy DM, Kotchmar DJ. Synthesis of environmental evidence: nitrogen dioxide epidemiology studies. *J Air Waste Manage Assoc*. 1992;42:662-671.

20. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994;50:1088-1101.

21. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629-634.

22. Cochran WG. The combination of estimates from different experiments. *Biometrics*. 1954;8:101-129.

23. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177-188.

24. Facon T, Mary JY, Harousseau JL, et al. Front-line or rescue autologous bone marrow transplantation (ABMT) following a first course of high dose melphalan (HDM) in multiple myeloma (MM)—preliminary results of a prospective randomized trial (CIAM protocol). *Blood* 1996;88(suppl 1):685a. Abstract 2729.

25. Fermand JP, Ravaud P, Chevret S, et al. High-dose therapy and autologous peripheral blood stem cell transplantation in multiple myeloma: up-front or rescue treatment? Results of a multicenter sequential randomized clinical trial. *Blood*. 1998;92:3131-3136.

26. Segeren CM, Sonneveld P, van der Holt B, et al. Overall and event-free survival are not improved by the use of myeloablative therapy following intensified chemotherapy in previously untreated patients with multiple myeloma: a prospective randomized phase 3 study. *Blood*. 2003;101:2144-2151.

27. Palumbo A, Bringhen S, Petrucci MT, et al. Intermediate-dose melphalan improves survival of myeloma patients aged 50 to 70: results of a randomized controlled trial. *Blood*. 2004;104:3052-3057.

28. Barlogie B, Kyle RA, Anderson KC, 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;24:929-936.

29. Facon T, Mary J, Harousseau J, et al. Superiority of melphalan-prednisone (MP) + thalidomide (THAL) over MP and autologous stem cell transplantation in the treatment of newly diagnosed elderly patients with multiple myeloma. In: *Proceedings of the ASCO*; 2006. Available at: http://www.asco.org.portal./site/ASCO/menuitem.64cfbd0f85cb37b2eda2be0agee37a01d/?vgnextoid=09f8201eb61a7. Accessed July 7, 2006.

30. Chalmers I, Matthews R. What are the implications of optimism bias in clinical research? *Lancet*. 2006;367:449-450.

31. Moreau P, Facon T, Attal M, et al. Comparison of 200 mg/m(2) melphalan and 8 Gy total body irradiation plus 140 mg/m(2) melphalan as conditioning regimens for peripheral blood stem cell transplantation in patients with newly diagnosed multiple myeloma: final analysis of the Intergroupe Francophone du Myelome 9502 randomized trial. *Blood*. 2002;99:731-735.

32. Attal M, Harousseau JL, Facon T, et al. Single versus double autologous stem-cell transplantation for multiple myeloma. *N Engl J Med*. 2003;349:2495-2502.

33. Stadtmauer EA. Multiple myeloma, 2004—one or two transplants? *N Engl J Med*. 2003;349:2551-2553.

34. Crawley C, Lalancette M, Szydlo R, et al. Outcomes for reduced-intensity allogeneic transplantation for multiple myeloma: an analysis of prognostic factors from the Chronic Leukaemia Working Party of the EBMT. *Blood*. 2005;105:4532-4539.

35. Maloney DG, Molina AJ, Sahebi F, et al. Allografting with nonmyeloablative conditioning following cytoreductive autografts for the treatment of patients with multiple myeloma. *Blood*. 2003;102:3447-3454.

36. Richardson PG, Sonneveld P, Schuster MW, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. *N Engl J Med*. 2005;352:2487-2498.

37. Rajkumar SV, Hayman SR, Lacy MQ, et al. Combination therapy with lenalidomide plus dexamethasone (Rev/Dex) for newly diagnosed myeloma. *Blood*. 2005;106:4050-4053.

38. Richardson P, Anderson K. Thalidomide and dexamethasone: a new standard of care for initial therapy in multiple myeloma. *J Clin Oncol*. 2006;24:334-336.