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High-Dose Chemotherapy with Early Autologous Stem Cell Transplantation Compared to Standard Dose Chemotherapy or Delayed Transplantation in Patients with Newly Diagnosed Multiple Myeloma: A Systematic Review and Meta-Analysis

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Autologous stem cell transplantation (SCT) is the standard of care for all transplantation-eligible patients diagnosed with multiple myeloma (MM). Various studies have compared clinical outcomes with frontline SCT ("early SCT") versus standard-dose therapy (SDT) alone, with or without salvage SCT ("SDT/late SCT"). In this meta-analysis, we compare overall survival (OS) and progression-free survival (PFS) outcomes between these 2 treatment approaches. Twelve studies were identified, including a total of 3633 patients, of whom 1811 received early SCT and 1822 received SDT/late SCT. In our analysis of all 12 studies, OS was not significantly different between the 2 groups (hazard ratio [HR], .86; 95% confidence interval [CI], .70 to 1.04), but PFS was better with early SCT (HR, .67; 95% CI, .54 to .82). In a subgroup analysis of 3 studies in which novel agents were used for induction, OS again was similar in the 2 groups, and PFS was favorable with early SCT (HR, .50; 95% CI, .36 to .70). This analysis shows that over the years, early SCT has been associated with prolonged PFS, but this did not consequently translate into prolonged OS in patients with newly diagnosed MM. The benefit of early SCT in terms of OS is less clear in the era of novel agents, given the limited follow-up of these studies.

INTRODUCTION

High-dose therapy (HDT) with autologous stem cell transplantation (SCT) following induction therapy has been the standard treatment for multiple myeloma (MM) in transplantation-eligible patients since the 1990s. When this approach was studied in the 1980s, HDT with SCT led to higher rates of complete response, which translated into prolonged duration of remission [1,2]. HDT with SCT can be in the form of a single course of HDT followed by stem cell rescue or a tandem approach in which 2 planned SCTs are conducted serially. This approach of HDT therapy with SCT following induction at diagnosis ("early SCT") has yielded varying results in terms of progression-free survival (PFS) and overall survival (OS) in patients with newly diagnosed MM compared with standard-dose therapy (SDT) alone, with or without SCT for salvage in this setting ("SDT/late SCT") [3-14].

As the armamentarium for treatment of MM has evolved in recent years, the utility of this approach has been called into question. Moreover, the timing of HDT and SCT as part of upfront therapy for newly diagnosed MM or as salvage therapy on relapse has been under debate. Various randomized trials that have examined this question have yielded variable results over the years, likely due to differences in patient selection and treatment regimens in these trials. Most recently, a randomized controlled trial continued to show an improvement in PFS despite the use of novel agent therapies for induction, although an improvement in OS was not noted with the available follow-up [4]. In addition, despite the advances in therapeutic options, novel agents and autologous SCT are not available uniformly worldwide due to access, affordability, or social issues [15]. Thus, the issue of early SCT compared with SDT in these patients remains pertinent.

We conducted the present meta-analysis and systematic review to examine patterns of OS and PFS with the early SCT

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versus SDT/late SCT approaches in patients with newly diagnosed MM.

METHODS

Data Sources and Searches

We conducted a thorough search to identify randomized controlled trials comparing early SCT versus SDT/late SCT in patients with newly diagnosed MM. A literature search was conducted from database inception through October 1, 2017, with electronic databases such as MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL). To identify relevant citations, we used various combinations of the terms, including "autologous stem cell transplantation," "multiple myeloma," "high dose therapy," "conventional chemotherapy," "standard dose therapy," "early transplantation," "late transplantation," and "plasma cell disorders." Two reviewers (T.J. and M.B.S.) identified articles eligible for further review by performing a screen of abstracts and titles. Full articles/manuscripts were obtained and reviewed for relevant studies to include in the meta-analysis based on the inclusion criteria elaborated below. In addition, previous meta-analysis and systematic review studies were reviewed to identify any additional studies.

Selection Criteria

We included randomized clinical trials that reported outcomes of patients (OS and PFS) who underwent early SCT versus SDT/late SCT, in patients with newly diagnosed MM. These criteria applied for both systematic review and the meta-analysis. Studies published in English language in adult patients age >18 years were included. Endnote version X8 (Clarivate Analytics, Philadelphia, PA) was used to manage literature obtained from the initial search, and duplicates were identified and excluded. Only studies on human subjects were included. The remaining literature was screened by scanning titles and abstracts, applying the following exclusion criteria: (1) review or meta-analysis, (2) retrospective or nonrandomized control study, (3) single-arm study without a comparative group, (4) abstract-only reports, and (5) study using allogeneic SCT alone or done in patients with relapsed/refractory MM.

Data Collection and Outcome Measures

We extracted prespecified data elements from each study, including patient demographics and baseline characteristics, sample size, therapeutic agents used, and outcomes data for OS as well as PFS. Corresponding authors for respective studies were contacted for any additional information, if necessary. Primary end outcomes of interest were OS and PFS. Information on baseline cytogenetics and treatment-related mortality (TRM) was also obtained when available.

Risk of Bias and Quality Assessment

Two authors independently evaluated included studies for methodological features that protected their results from bias. The Cochrane risk of bias assessment was used for assessing the quality of randomized controlled trials included in the meta-analysis.

Statistical Analysis and Data Synthesis

From each study, we obtained the relative association measure and 95% confidence interval (CI). We chose the random-effects method as primary analysis because of its conservative summary estimate and incorporation between-study and within-study variance using the using the DerSimonian method [16]. We used the hazard ratio (HR) provided by the included studies to conduct a pooled HR for survival outcomes. An estimate of the log HR can be obtained from statistics computed during a log-rank analysis; also, the log HR is estimated only approximately, and in some reviews, it was referred to as a log odds ratio [17].

We used the I^2 statistic to assess for heterogeneity across the included studies. An I^2 value >50% suggests substantial heterogeneity between studies [18]. A sensitivity analysis was conducted after removing the studies that performed tandem transplantations for their included patients with MM. Another sensitivity analysis was performed to estimate the influence of each study by deleting each trial in turn from the analysis and noting the degree to which the effect size and significance of the treatment effect changed. This analysis was performed for both OS and PFS. We considered a study influential if the exclusion of it changed our conclusion or the effect estimate by at least 20% pooled outcomes. We conducted subgroup analyses for different subsets of patients who received novel therapeutic agents for induction therapy in both arms. The threshold for statistical significance was set at $P < .05$ for effect sizes. Statistical analyses were conducted using RevMan version 5.3 (The Nordic Cochrane Center, Copenhagen, Denmark). The study was performed in accordance with the recommendations set forth by the PRISMA work groups [19].

RESULTS

Twelve studies were eligible for inclusion in this meta-analysis and systematic review [3-14]. Figure 1 elaborates the details of inclusion strategy leading to the selection of these studies. A total of 3633 patients were included in the analysis of these 12 studies, including 1822 who underwent early SCT and 1811 who underwent SDT/late SCT. All studies were randomized control trials that enrolled patients with newly diagnosed MM. Four studies included a tandem SCT strategy as a part of the HDT/SCT group [8,11-13]. In the IFM 9906 study [8], 2 arms received SDT, including 1 arm that received melphalan with prednisone and 1 arm that received melphalan, prednisone, and thalidomide. The latter arm was included in the main analysis, although a sensitivity analysis was done to include the other arm as well, and no change in overall outcome was noted. Of note, IFM 9906 was done in patients age 65 to 75 years and used a melphalan dose of 100 mg/m^2 for conditioning before SCT in both arms. The M97G trial was conducted in patients age 50 to 70 years and used melphalan 100 mg/m^2 before SCT [12]. Details of patient enrollment and treatment designs for all studies are provided in Table 1.

High-risk cytogenetics information was included only in the more recent studies [4,8,11,13] (Supplementary Table 1). We included del 17p, t(4;14) or t(14;16), if reported, as high-risk cytogenetics for description in this meta-analysis [20,21]. These appeared to be balanced in the 2 arms in the various studies and ranged between 17% and 28% in each arm.

The risk of bias assessment using the Cochrane risk of bias tool showed a moderate risk of bias overall (Supplementary Table 2).

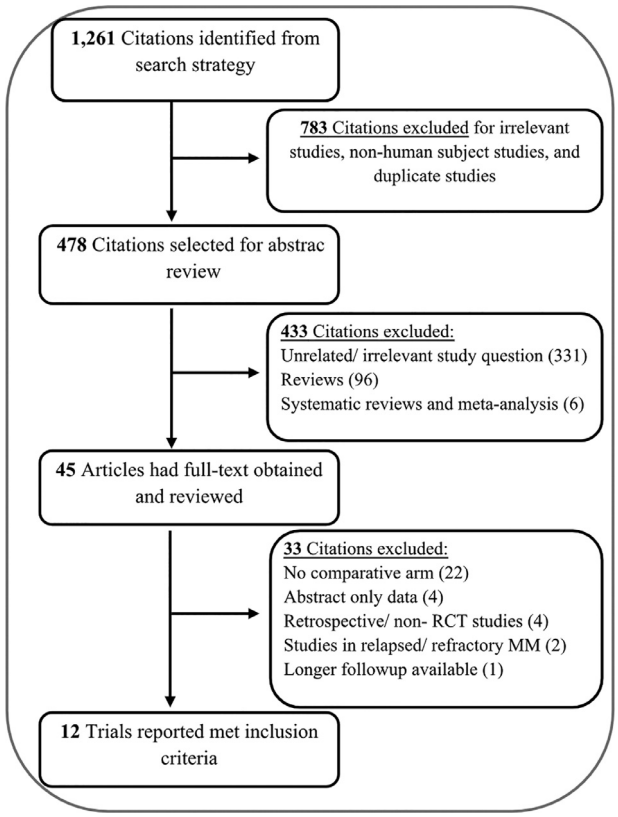


Figure 1. Flowchart of screening and selection of relevant studies. RCT, randomized controlled trial.

Table 1
Baseline Characteristics and Details of Included Studies

Study	Enrollment Period	Randomization (n of Patients)	Age, yr, mean ± SD or median (range)	Number of Centers	Staging Category at Diagnosis, %	Chemotherapy Regimen	Use of Novel Agents with Induction	Conditioning Regimen for SCT	Maintenance	Patients Who Underwent Treatment in the Non-HDT Arm, n/N (%)	Median Follow-Up, mo
Attal et al, 1996 (IFM 90) [3]	10/1990- 5/1993	(A) Standard-dose chemotherapy (100)	(A) 58 ± 5.2	33	(A) DS III, 77	(A, B) VMCP/BVAP 4-6 cycles	No	Mel 140 mg/m^2 + TBI 8 Gy in 4 fractions	INF-α in the SCT cohort	9/100 (9)	37
		(B) Early SCT (100)	(B) 57 ± 6.4		(B) DS III, 72						
Fermand et al, 1998 (MAG 90) [10]	1/1990- 6/1995	(A) Standard-dose chemotherapy with late (R/R) SCT (94)	(A) 48 ± 5	14	(A) DS III, 82	(A) VMCP	No	Lomustine day -8, VP16 days -8 to -6, Cy day -4, Mel day -4, TBI days -3 to -1	INF-α to both arms until tolerated	73/94 (78)	58
		(B) Early SCT (91)	(B) 47 ± 5		(B) DS III, 87	(B) VAMP					
Child et al, 2003 (MRC7) [7]	10/1993- 10/2000	(A) Standard-dose chemotherapy (200)	(A) 56 (35-64)	83	(A) ISS III (with β2 micro >4), 50	(A) Dox, carmustine, Cy, Mel	No	Mel 200	INF-α-2a maintenance in both arms	30/200 (15)	42
		(B) Early SCT (201)	(B) 55 (33-66)		(B) ISS III, 54	(B) Dox, vincristine, methylprednisone, Cy					
Palumbo et al, 2004 (M97G) [12]	10/1997- 12/2000	(A) Standard-dose chemotherapy (99)	(A) 56 (35-64)	18	(A) DS III, 62	(A) Oral Mel, prednisone	No	Mel 100 × 2	INF and Dex in responders	37/99 (37)	(A) 39
		(B) Early SCT (95)	(B) 55 (33-66)		(B) DS III, 61	(B) Dex, Dox, vincristine					(B) 41
Fermand et al, 2005 (MAG91) [9]	11/1991- 9/1998	(A) Standard-dose chemotherapy (96)	(A) 60 (58-62)	14	(A) DS III, 82	(A) VMCP	No	Mel 200 or Mel 140 + busulfan 16 mg/kg p.o.	No	22	120
		(B) Early SCT (94)	(B) 61 (59-63)		(B) DS III, 79	(B) CHOP followed by VAMP					
Bladé et al, 2005 (PETHEMA) [6]	5/1994- 10/1999	(A) Standard-dose chemotherapy (83)	(A) 56	29	(A) DS III, 82	(A, B) VBMCP/VBAD	No	Mel 200, Mel 140 + TBI 12 Gy in 4 fractions	INF and Dex in responders	10/83 (12)	56
		(B) Early SCT (81)	(B) 57		(B) DS III, 79						
Barlogie et al, 2006 (S9321) [5]		(A) Standard-dose chemotherapy (255)	(A) 54.3 (28.3-69.5)		(A) DS III, 56	(A) VAD followed by VBMCP	No	Mel 140 + TBI 12 Gy	INF by randomization	87/225 (39)	76
		(B) Early SCT (261)	(B) 54.6 (30.9-70.6)		(B) DS III, 57	(B) VAD					
Facon et al, 2007 (IFM 99-06) [8]	5/2000-8/2005	(A) Standard-dose chemotherapy (125)	(A) 40% >70 yr	73	(A) ISS III 29	(A) Mel, prednisone thalidomide	Yes (thalidomide only in SDT arm)	Mel 100 × 2	No	12 from both MP and MPT arms	36.8
		(B) Early SCT (126)	(B) 39% >70 yr		(B) ISS III, 35%	(B) VAD					

(*continued on next page*)

Table 1 (*Continued*)

Study	Enrollment Period	Randomization (n of Patients)	Age, yr, mean ± SD or median (range)	Number of Centers	Staging Category at Diagnosis, %	Chemotherapy Regimen	Use of Novel Agents with Induction	Conditioning Regimen for SCT	Maintenance	Patients Who Underwent Treatment in the Non-HDT Arm, n/N (%)	Median Follow-Up, mo
Sonneveld et al, 2007 [14]	11/1995- 3/2000	(A) Standard-dose chemotherapy (148)	(A) 55 (37-65)	46	(A) DS III, 74%	(A) VAD, Mel 70 × 2 without stem cell rescue	No	Cy + TBI	INF	NA	92
		(B) Early SCT (155)	(B) 56 (32-65)		(B) DS III, 75%	(B) VAD, Mel 70 × 2					
Palumbo et al, 2014 [12]	11/2007- 7/2009	(A) Standard-dose chemotherapy (132)	(A) 57 (51-61)	62	(A) ISS III, 22%	(A) RD followed by consolidation with MPR	Yes	Mel 200 × 2	Len by randomization	98/132 (74)	51.2
		(B) Early SCT (141)	(B) 57 (50-61)		(B) ISS III, 16.3	(B) RD					
Gay et al, 2015 [11]	7/2009-5/2011	(A) Standard-dose chemotherapy (129)	(A) 56 (51-61)	59	(A) RISS III, 5	(A) RD followed by consolidation with Cy, Dex, and Len	Yes	Mel 200 × 2	Len versus Len + prednisone by randomization	53/129 (41)	52
		(B) Induction chemotherapy followed by early SCT (127)	(B) 57 (53-62)		(B) RISS III, 3	(B) RD					
Attal et al, 2017 [4]	7/2009- 5/2011	(A) Standard-dose chemotherapy (350)	(A) 60 (30-66)	69	(A) ISS II ,19	(A) RVD induction, RVD consolidation	Yes	Mel 200	Len, bortezomib	136/350 (39)	(A) 44
		(B) Early SCT (350)	(B) 59 (29-66)		(B) ISS III, 17	(B) RVD					(B) 43

DS, Durie Salmon (Stage) indicates; VMCP, vincristine, melphalan, cyclophosphamide, prednisone; BVAP, vincristine, carmustine, doxorubicin, prednisone; Mel, melphalan; TBI, total body irradiation; Cy, cyclophosphamide; ISS, International Staging System; Dox, doxorubicin; Dex, dexamethasone; CHOP, Cyclophosphamide, Hydroxydaunorubicin, Oncovin (Vincristine), Prednison; VAD, Vincristin, Adriamycin, Dexamethasone; Len, lenalidomide; VAMP, vincristine, doxorubicin, i.v. methylprednisone; VBMCP, vincristine, BCNU, melphalan, cyclophosphamide, prednisone; VBAD, vincristine, BCNU, adriamycin, dexamethasone; RD, Revlimid, Dexamethasone; MPR, melphalan, prednisone, lenalidomide; RISS, Revised International Staging System; RVD, Revlimid, Bortezomib (Velcade), Dexamethasone.

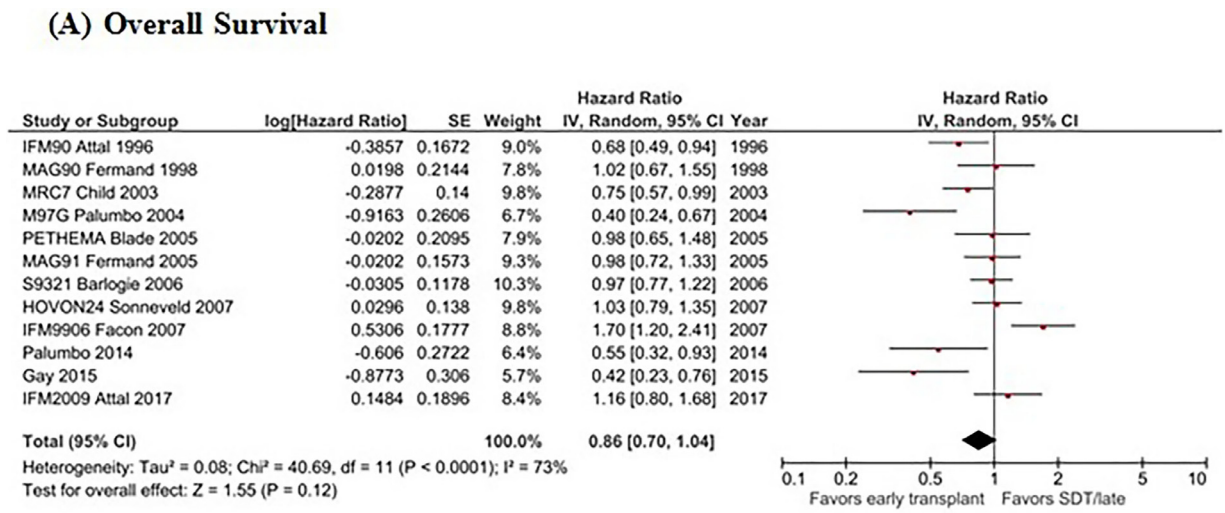
Table 2
Comparison of TRM and Response Rates

Study	TRM, %		Complete Response, %		ORR (≥PR)	
	SDT/Late SCT	Early HDT/ SCT	SDT/Late SCT	Early HDT/ SCT	SDT/Late SCT	Early HDT/ SCT
Attal et al, 1996 (IFM 90) [3]	5	7	5	22	57	81
Fermand et al, 1998 (MAG 90) [10]	14	10	5	17	62	86
Child et al, 2003 (MRC7) [7]	NA	3	8	44	48	86
Palumbo et al, 2004 (M97G) [12]	NA	NA	NA	NA	42	72
Fermand et al, 2005 (MAG91) [9]	2	0	20	36	58.5	62
Bladé et al, 2005 (PETHEMA) [6]	NA	NA	15	14	83	82
Barlogie et al, 2006 (S9321) [5]	.4	3	15	17	90	93
Facon et al, 2007 (IFM 99-06) [8]	0	5	13	18	76	65
Sonneveld et al, 2007 [14]	4	10	9	26	NA	NA
Palumbo et al, 2014 [12]	NA	NA	18.2	23.4	90.9	92.9
Gay et al, 2015 [11]	1.5	.8	20	32	89	91
Attal et al, 2017 [4]	.6	1.7	48	59	79	88

ORR indicates overall response rate; PR, partial response.
*SDT arm: melphalan, prednisone, and thalidomide.

OS Differences

OS was reported in all studies, and a pooled analysis showed no statistically significant differences in OS between the 2 approaches (HR, .86; 95% CI, .70 to 1.04) (Figure 2A). To establish the robustness of this analysis, we performed sensitivity analysis by removing individual studies. Removing IFM



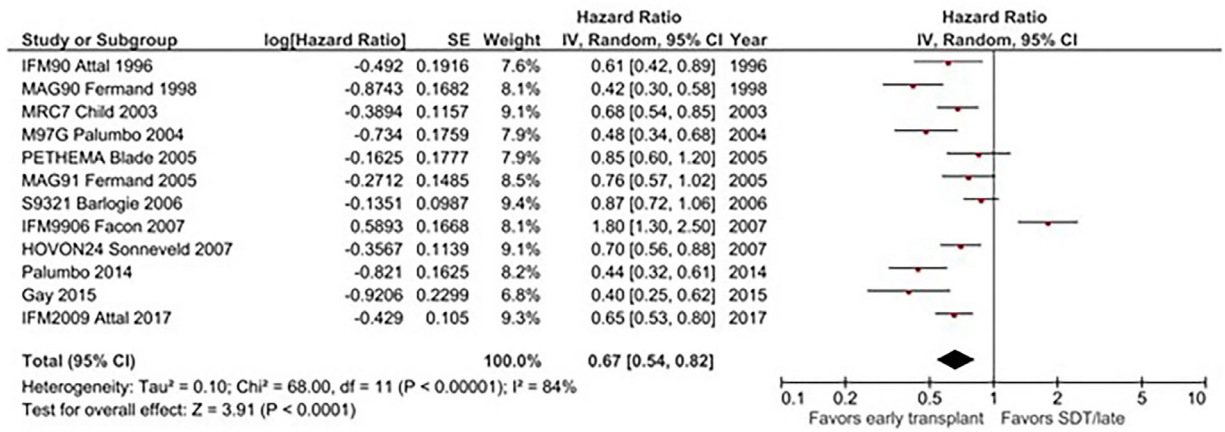


Figure 2. OS and PFS for all studies.

9906 changed the HR to .81 (95% CI, .68 to .97), which was then favorable toward early SCT (Supplementary Figure 1A). We also performed a sensitivity analysis after exclusion of studies that performed tandem transplantation as a part of the HDT/SCT. There was no change in the overall outcome of OS (HR, .92; 95% CI, .82 to 1.04) (Supplementary Figure 1B).

PFS

PFS was also reported in all studies, and a combined analysis revealed a statistically significant benefit with the early SCT approach (HR, .67; 95% CI, .54 to .82) (Figure 2B). In a sensitivity analysis, exclusion of individual studies did not change in the overall outcome of PFS, which remained favorable toward an early SCT approach. On exclusion of the 4 studies that used a tandem transplantation approach, PFS remained significantly favorable toward the early SCT arm (combined HR, .69; 95% CI, .60 to .79) (Supplementary Figure 2).

Use of Novel Agents

A subgroup analysis was conducted for the 3 studies including novel agents with the induction regimen. The novel agents included in these studies were lenalidomide alone in 2 studies [11,13] and a combination of lenalidomide and bortezomib in 1 study [4]. The IFM9906 study used a novel agent, thalidomide, in the SDT arm; however, this was not included in the subgroup of novel agents, because thalidomide was used only in the SDT arm, whereas patients in the early SCT arm received vincristine, adriamycin, and dexamethasone as induction therapy.

As shown in Figure 3, OS remained statistically nonsignificant between the early SCT and SDT/late SCT arms (HR, .66; 95% CI, .35 to 1.27) in the combined analysis of studies using novel agents. In studies not using novel agents for induction therapy, OS was still not statistically significantly different (Figure 3). PFS analysis showed a combined HR of .50 (95% CI, .36 to .70) for the 3 studies, indicating the statistically significant advantage of the early SCT approach (Figure 4). In the studies in which no novel agents were used in induction regimens, PFS was still statistically significantly better in the early SCT arm (HR, .73; 95% CI, .58 to .93) (Figure 4).

TRM and Response Rates

Details of TRM, complete response rates, and overall response rates are provided in Table 2. As expected, TRM has improved in the more recent studies compared with older studies; with less use of the more toxic traditional chemotherapy and improved supportive care. In the more recent studies, TRM with either approach was low, <2 % [4,11]. Complete response and overall response rates remained better with the early SCT approach.

DISCUSSION

Our meta-analysis including all studies addressing early SCT versus SDT/late SCT shows that although there is a PFS advantage with the former approach, this does not present as an OS benefit with early SCT. Similar results were shown when using novel agents, with no OS benefit noted with early SCT over SDT/late SCT. It must be noted, however, that an OS benefit with early SCT was seen in 2 individual studies using novel agents for induction followed by 2 rounds of HDT/SCT [11,13]. In the third study using novel agents, non-statistically significant differences in OS were reported for up to 4 years [4]. The median OS in patients in the novel agent era at the time of enrollment of this study (2010 to 2012) has been reported to exceed 6 years [22]; thus, the follow-up in this study might not have been long enough to identify differences in OS. Nevertheless, in the studies using novel agent therapies, PFS remained statistically significantly better with early SCT in patients with newly diagnosed MM. The response rate and complete response rate were consistently numerically higher in the early SCT arm compared with the SDT/late SCT arm in all studies, reflecting the deeper response imparted by early SCT. Our meta-analysis data indicate that SCT continues to have a significant role in the treatment armamentarium for MM by providing a more durable remission.

Despite the various studies showing a benefit of early SCT, the use of this therapy remains low, as has been shown in

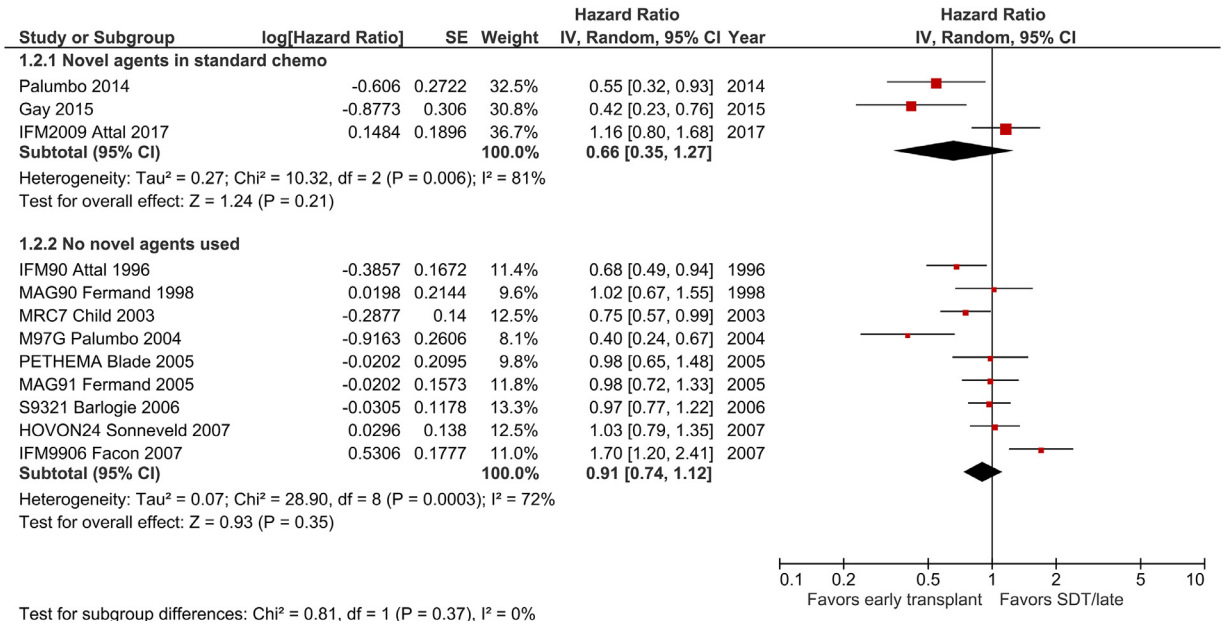


Figure 3. Subgroup analysis of OS for studies using novel agents for induction and those not using novel agents.

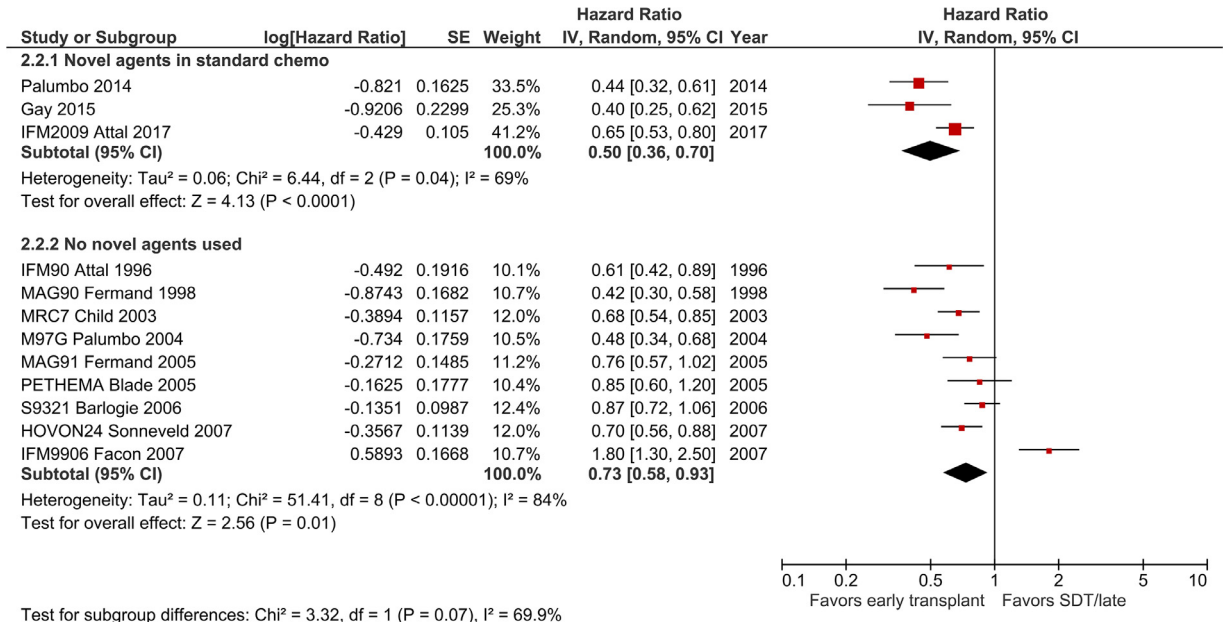


Figure 4. Subgroup analysis of PFS for studies using novel agents for induction and those not using novel agents.

Center for International Blood and Marrow Transplant Research data and the National Cancer Database [23,24]. Certain factors, including ethnicity, socioeconomic barriers, geographical location, and medical insurance issues, seem to be associated with the underuse of this effective and safe modality in incurable hematologic malignancies. As shown in Supplementary Table 3, responses with early SCT have been consistently better and the risk of mortality has been similar to that of SDT/late SCT. In fact, TRM from early SCT has been <2% in the more recent studies [4,11]. This shows that even in the era of novel agents, early SCT remains a safe and effective treatment, and that the availability and use of SCT need improvement. In addition, value considerations will need to be incorporated into the decision making regarding the best use and timing of SCT along with novel therapies.

Having said that, however, HDT/SCT is clearly not curative for the majority of patients with MM. None of the studies that we evaluated included the newer novel agents, such as carfilzomib or daratumumab, which have the potential to provide the deeper response that we aim to achieve with SCT [25-28]. Whether using these agents in frontline therapy can substitute for the need for early SCT remains to be studied in a clinical trial setting. With the ever-evolving therapeutic paradigm in MM, the role of SCT will continue to remain a matter of debate. However, at a global level, where the use of novel agents remains sparse in many areas due to availability or affordability issues, early SCT continues to have an important role and should be considered in all transplantation-eligible patients, given the statistically significant PFS benefit and higher responses.

The lack of OS advantage in the overall analysis leads us to theoretically hypothesize that SCT may become dispensable for the initial therapy for MM. As shown in Table 1, a varying percentage of patients in the SDT/late SCT arm did not require HDT/SCT until the last follow-up in the respective studies. This is clinically significant, because there is not only a low risk of TRM from HDT/SCT, but also concern regarding the long-term risk of therapy-related myelodysplastic syndrome and/ or acute myelogenous leukemia with HDT [29,30]. The latter is even more meaningful in the current era, given that the average survival of patients with MM is increasing to almost a decade owing to improved therapies [22].

Minimal residual disease (MRD) testing is an emerging concept in the field of MM, and negative MRD status has been correlated with improved prognosis in various studies irrespective of the therapy used [31-33]. Currently, this strategy has mostly been evaluated in patients who have undergone SCT. Some studies testing MRD after initial induction have also shown superior outcomes in patients with no MRD, including transplantation-ineligible patients [34,35]. These and future studies may help establish the role of MRD after induction to determine the optimal timing of HDT/SCT in an individual patient. Currently, the integration of MRD testing into treatment decision making is not recommended outside the setting of a clinical trial.

Our results are along the lines of a recently published meta-analysis including studies using only novel agents that showed a PFS benefit in patients undergoing early SCT even in the era of novel agent therapies with only slight differences in inclusion criteria [36]. We did not include abstracts in our meta-analysis, because the data are not peer-reviewed at that stage, which led to the exclusion of 2 abstracts evaluating a similar question. One of these abstract, a study by Cavo et al [37] recently presented at annual meeting of American Society of Hematology, showed improved PFS with early SCT compared with the SDT arm receiving bortezomib, melphalan, and prednisone. The final publication of this study is awaited to provide more insight into its nuances.

The present meta-analysis is an update of a previous meta-analysis reported by Koreth et al [38] performed almost a decade ago for then-current studies. Since then, there have been 3 additional studies [4,11,13], and longer follow-up or peer-reviewed published data are available for 2 studies [8,14], which have been updated in this meta-analysis. The results from our subgroup analysis not including novel agents are comparable to those of the analysis conducted in the era in which novel agents were not included in most studies, showing a PFS benefit without an OS benefit.

As with any meta-analysis, our present meta-analysis has some limitations owing to the heterogeneity of the included

studies as measured by the I^2 statistic. Because of the widely varying time range and location of these studies, the treatment regimens used in induction also varied among the trials, although they were balanced between the 2 arms of the meta-analysis. In addition, some of the studies included in this meta-analysis include pre-novel agent era drugs. However, although these regimens are not commonly used in the United States, these novel agents are still available sparingly worldwide, and questions about the use of these older regimens still have value [15]. In addition, patients who were treated with older regimens were distributed similarly in the 2 arms, thus addressing the primary question of early SCT versus late SCT.

It is difficult to account for all these differences in such a meta-analysis. Nevertheless, using data from a combined analysis of more than 3500 patients, we show that early SCT provides an PFS advantage, albeit without an apparent OS advantage.

CONCLUSION

The data from our meta-analysis show a PNS benefit but no OS benefit of an early SCT approach in patients with newly diagnosed MM. In the studies using novel agents, a statistically significant PFS benefit but not a statistically significant OS benefit, possibly owing to limited follow-up in some recent studies. Although SCT should be offered to all transplantation-eligible patients with newly diagnosed MM, the advantage in the era of the novel agents will continue to be evaluated.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.bbmt.2018.09.021.

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