Tandem Versus Single Autologous Hematopoietic Cell Transplantation for the Treatment of Multiple Myeloma: A Systematic Review and Meta-analysis

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Background Evidence bearing on the efficacy of tandem autologous hematopoietic transplant (AHCT) vs a single AHCT in patients with multiple myeloma (MM) is conflicting. We performed a systematic review and meta-analysis to synthesize the existing evidence related to the effectiveness of tandem vs single AHCT in patients with MM.

Methods We searched Medline, conference proceedings, and bibliographies of retrieved articles and contacted experts in the field to identify randomized controlled trials (RCTs) reported in any language that compared tandem with single AHCT in patients with MM through March 31, 2008. Endpoints were overall survival (OS), event-free survival (EFS), response rate, and treatment-related mortality (TRM). Data were pooled under a random-effects model.

Results Six RCTs enrolling 1803 patients met the inclusion criteria. Patients treated with tandem AHCT did not have better OS (hazard ratio [HR] for mortality for patients treated with tandem transplant vs single transplant = 0.94; 95% confidence interval [CI] = 0.77 to 1.14) or EFS (HR = 0.86; 95% CI = 0.70 to 1.05). Response rate was statistically significantly better with tandem AHCT (risk ratio = 0.79, 95% CI = 0.67 to 0.93), but with a statistically significant increase in TRM (risk ratio = 1.71, 95% CI = 1.05 to 2.79). There was statistically significant heterogeneity among RCTs for OS and EFS.

Conclusion In previously untreated MM patients, use of tandem AHCT did not result in improved OS or EFS. We conclude that tandem AHCT is associated with improved response rates but at risk of clinically significant increase in TRM.

J Natl Cancer Inst 2009;101:100–106

Autologous hematopoietic cell transplantation (AHCT) after high-dose chemotherapy has been the predominant treatment for patients with multiple myeloma (MM) who are considered transplant candidates (1). The role of AHCT in the management of MM has been evaluated in several randomized controlled trials (RCTs) that initially indicated a survival advantage with AHCT over conventional treatment (2,3). However, a recent systematic review and meta-analysis of RCTs showed a beneficial outcome for event-free survival (EFS), but not for survival associated with single AHCT, relative to conventional treatment (4).

Building on the initial success of single AHCT, a more intense approach using tandem AHCT was proposed to lead to further improvements in therapeutic outcomes (5). The first RCT published in 2003 by Attal et al. (6) reported that tandem AHCT improved overall survival (OS) and EFS in patients with MM. Subsequently, several RCTs have assessed the efficacy of tandem autologous transplants vs a single transplant in patients with MM (7,8). The results from these RCTs were conflicting. Because decision making should not depend on the results from selective trials, we conducted a systematic review and meta-analysis to comprehensively assess the existing evidence related to the relative benefits and harms of tandem AHCT vs single AHCT in patients with previously untreated MM.

We used the comprehensive search strategies described by Dickersin et al. (9) to identify all relevant RCTs through March 31, 2008, in the Medline (PubMed) electronic database. We also performed manual searches of abstracts from the annual meetings of the American Society of Hematology (1993–2007), American Society for Clinical Oncology (1993–2007), proceedings of the International Myeloma Foundation Workshops (2003–2007), and

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DOI: 10.1093/jnci/djn439

the European Hematology Association (1993–2007) to identify potential RCTs. In addition, experts in the field were contacted to identify unpublished data in this subject area. No search limits were applied on the basis of language. Studies were included if they were prospective RCT comparing tandem AHCT vs single AHCT in patients with previously untreated MM and reported OS and/or EFS, response rates, and treatment-related mortality (TRM) on an intention-to-treat basis.

Two reviewers (A. Kumar and B. Djulbegovic) independently screened the titles and abstracts of all identified studies to assess their eligibility for inclusion. These reviewers extracted data on benefits (in terms of OS, EFS, and response rate) and harms (as reflected by TRM) of the two treatments. We also extracted data on the methodological domains relevant to minimizing bias and random error (namely, generation of allocation sequence, description of dropouts, and analysis on an intention-to-treat basis) in the conduct and analysis of the trials (10,11). There were no discrepancies in data extraction between the reviewers.

To compare tandem AHCT with single AHCT, both time-to-event (OS and EFS) and dichotomous data (response rate and TRM) were pooled and reported as hazard ratios and risk ratios (12), respectively, using a 95% confidence interval (CI) under a random-effects model (13). If time-to-event data were unavailable for direct extraction, we extracted data according to the method described by Parmar et al. (14). This method allows calculation of the hazard ratio from different parameters using indirect calculation of the variance and the number of observed minus expected events. We tested for heterogeneity using the χ^2 (13) and I^2 (15) tests. The possibility of publication bias was also assessed using the Begg and Egger funnel plot method (16,17). The meta-analysis was performed using Review Manager Version 5 for Windows software (18). The work was performed and reported according to the guidelines for Quality of Reporting of Meta-analyses (19). All statistical tests were two-sided (18).

Figure 1 outlines the process of identifying and selecting relevant studies to be included in the systematic review. The initial search yielded 419 citations, of which six were RCTs that compared tandem AHCT vs single AHCT in patients with MM (6–8,20–22). These trials enrolled a total of 1803 patients. Four of the six RCTs were reported in full (6–8,22), and the remaining two were reported as meeting abstracts (20,21).

We characterized the studies according to a set of factors that reflected their methodological rigor (Table 1). Overall, the studies were of good quality in that they were prospective randomized trials of adequate power, performed centralized assignment to treatments (ie, adequate allocation concealment), had sufficient description of dropouts, and analyzed on an intent-to-treat basis. The Begg and Egger funnel plot for the outcomes of OS (P = .198) showed a symmetric distribution indicating no publication bias.

For the primary endpoints of OS and EFS, data were available from all RCTs. For response rate, data were extractable from four RCTs. In two RCTs, the number of observed minus expected events and the variance were derived using the numbers of events in the experimental and control arms and the P values (6,8). In the remaining four RCTs, these quantities were calculated from the OS or EFS curve or the reported median survival

CONTEXT AND CAVEATS

Prior knowledge

Evidence from randomized controlled trials as to the relative efficacy of single vs tandem autologous hemopoietic cell transplantation in improving outcomes for patients with multiple myeloma was conflicting.

Study design

Meta-analysis in which overall survival (OS) and event-free survival (EFS) and response rate and treatment-related mortality (TRM) were pooled and reported as hazard ratios and risk ratios, respectively, using a random-effects model.

Contribution

The sum of the trial evidence did not suggest that OS or EFS was improved in patients who received tandem transplantation. Tandem transplantation improved response rates but led to increased TRM.

Implications

Routine use of tandem transplantation to treat patients with multiple myeloma is not justified.

Limitations

The study did not have access to individual patient data that may have helped to identify subgroups of patients who might benefit from tandem transplantation.

From the Editors

in the experimental and control arm and the associated P values (7,20,22,23).

The pooled results for OS showed no statistically significant benefit with the use of tandem AHCT (Figure 2). The hazard ratio for OS for patients treated with tandem transplant vs single transplant was 0.94 (95% CI = 0.77 to 1.14; P = .533; Figure 2). Similarly, for EFS, the hazard ratio for tandem transplant vs single transplant was 0.86 (95% CI = 0.70 to 1.05; P = .14; Figure 2) indicating no statistically significant benefit with the use of tandem AHCT. The response rate was statistically significantly better with tandem AHCT (risk ratio = 0.79, 95% CI = .0.67 to 0.93; P = .004; Figure 3). There was also statistically significant heterogeneity among trials in the estimates for OS and EFS (heterogeneity χ^2 = 11.66, P = .04, and heterogeneity χ^2 = 13.16, P = .02, for OS and EFS, respectively).

For the outcome of TRM, data were extractable from all but one RCT (21). The use of tandem AHCT was associated with a statistically significant increase in TRM (risk ratio = 1.71, 95% CI = 1.05 to 2.79; P = .03; Figure 3). Heterogeneity across all studies for TRM was not statistically significant (heterogeneity χ^2 = 1.40, P = .845).

We conducted sensitivity analysis to identify the reasons for the presence of heterogeneity for the outcomes of OS and EFS. In all included RCTs, random assignment was strictly to tandem vs single AHCT without maintenance or any other supportive therapies. However, in the trial by Abdelkefi et al. (22), random assignment was to single transplant plus maintenance therapy with thalidomide or tandem transplant. When the RCT by Abdelkefi et al. was excluded from the meta-analysis, the statistically significant

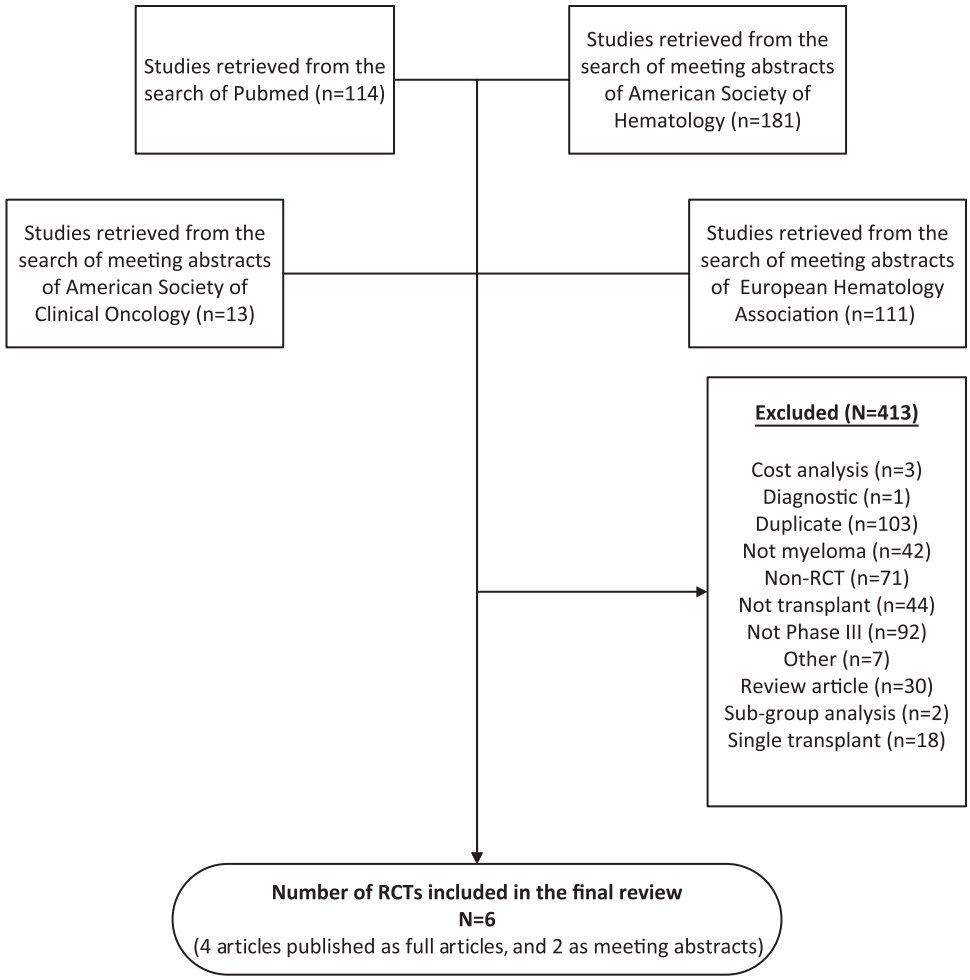


Figure 1. Flow diagram showing the process of identifying and selecting relevant studies.

heterogeneity disappeared for both outcomes. Excluding this study from the overall analysis did not result in a statistically significant difference between single and tandem AHCT for the outcome of OS (HR for tandem vs single AHCT = 0.89, 95% CI = 0.76 to 1.04, $P = .16$). However, exclusion of the study by Abdelkefi et al. (22) resulted in a statistically significant change in the hazard ratio for EFS (HR for tandem vs single AHCT = 0.79, 95% CI = 0.70, 0.89, $P < .001$) favoring tandem transplant.

Additional sensitivity analyses according to publication type (abstract vs full text) or reporting of sample size calculations (reported vs not) did not have any effect on the outcomes of OS and EFS. The hazard ratio for OS for patients treated with tandem transplant vs single transplant was 0.89 (95% CI = 0.66 to 1.99) in studies that did not report sample size calculations or reported as abstracts and 0.99 (95% CI = 0.74 to 1.33) in trials that reported these calculations and were reported in full. Similarly, the hazard ratio for EFS for patients treated with tandem transplant vs single transplant was 0.92 (95% CI = 0.73 to 1.15) in studies that did not report sample size calculations or published as abstracts vs 0.84 (95% CI = 0.63 to 1.11) in trials that reported them and were published as full text. There was no statistically significant heterogeneity among the compared subgroups.

Despite controversy as to the effectiveness of AHCT for MM, this disease is the most common indication for which single AHCT is used. Since the introduction of the concept of tandem AHCT by Barlogie et al. (5,24), there have been six RCTs performed that compared tandem and single AHCT (6–8,20–22). Our synthesis of data from these trials suggests that tandem AHCT does not result in improved OS or EFS as originally reported in the first trial. The available data do demonstrate improvement in response rates with use of tandem AHCT, but at the expense of a statistically significant increase in transplant-associated mortality with the tandem approach.

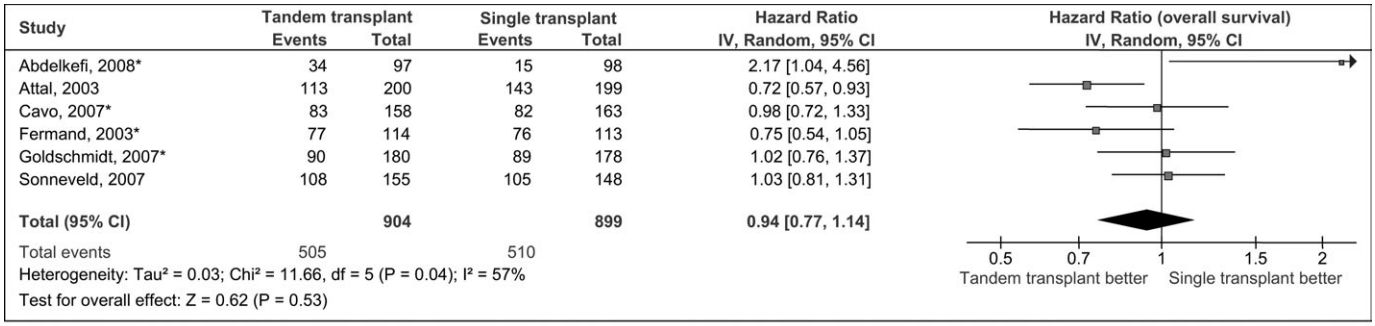
However, caution should be exercised when interpreting the results of our meta-analysis. First, two of the RCTs (20,21) did not report response rates, raising the possibility that response rates for the two approaches may not have been different. Second, failure to report TRM in one trial (21) may indicate that deaths associated with tandem transplant may have been worse than expected. Finally, EFS was a composite outcome in all the RCTs and was not uniformly reported among trials.

For the four RCTs that were published as complete reports, EFS definitions were available (6–8,22). The trials by Attal et al. (6) and Abdelkefi et al. (22) calculated the EFS from the day of random assignment to the time to progression, relapse, or death (the latter trial also used thalidomide maintenance in the single AHCT arm). However, in their trial, Sonneveld et al. (8) calculated EFS from the day of assignment until the determination of

Table 1. Characteristics of randomized controlled trials that have assessed the efficacy of tandem transplant vs single transplant in treatment of multiple myeloma*

Authors/year of publication	No. of patients	Median patient age		Percentage of patients with stage II-III disease		Median follow-up in months (range)	A priori sample size calculations performed	Publication type	More effective procedure (single versus tandem AHCT)			
		Tandem transplant	Single transplant	Tandem transplant	Single transplant				OS	EFS	Response rate	TRM
Abdelkefi et al. (2008) (22)	195	53	54	72%	70%	33 (6 to 46)	Yes	Full text	Single AHCT	Single AHCT	Neither	Neither
Attal (2003) (6)	399	52	52	93%	91%	75 (36 to 93)	Yes	Full text	Tandem AHCT	Tandem AHCT	Neither	Neither
Cavo et al. (2007) (7)	321	52.9	52.3	80%	80%	70 (32 to 112)	Yes	Full text	Neither	Tandem AHCT	Tandem AHCT	Neither
Fermand et al. (2005) (21)	227	50	50	97%	97%	73 (60 to 89)	Not reported	Abstract	Neither	Neither	Neither	Not reported
Goldschmidt (2007) (19)	358	56	55	Not reported	Not reported	Not reported	Not reported	Abstract	Neither	Neither	Not reported	Neither
Sonneveld et al. (2007) (8)	303	56	55	100%	100%	92 (17 to 129)	Yes	Full text	Neither	Tandem AHCT	Not reported	Neither

* The assignment to treatments in all included trials was performed centrally indicating adequate allocation concealment. All trials reported detailed data on patients who dropped out. The analysis was according to intention-to-treat in all trials. OS = overall survival; EFS = event-free survival; TRM = treatment-related mortality; AHCT = autologous hematopoietic cell transplant.



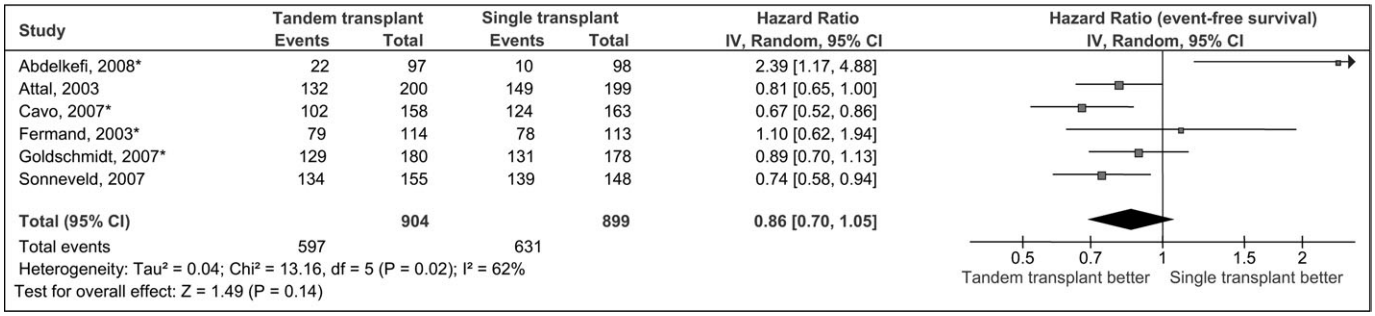
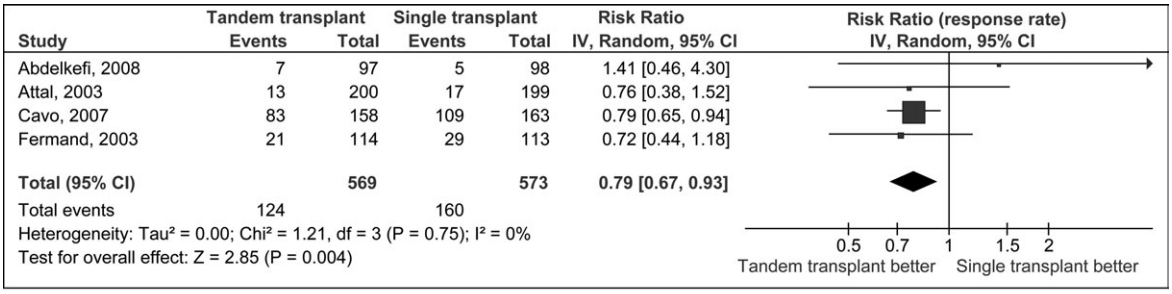


Figure 2. Forest plot of overall survival and event-free survival with tandem vs single transplant for myeloma. The summary effect estimate (hazard ratio) for individual randomized controlled trials are indicated by **black rectangles** (the size of the rectangle is proportional to the study weight), with the lines representing 95% confidence intervals (CIs). The overall summary effect estimate (hazard ratio) and 95% confidence interval are indicated by the **diamond** below. *The numbers of events are estimates and not the exact number of events.

the absence of at least a partial response after treatment with high-dose melphalan, progression or relapse after previous response, or death without progression, whichever came first. The RCT by Cavo et al. (7) calculated the EFS from the start of therapy to the date of relapse or progression or death from any cause. The definition of EFS is important because findings of statistically significant effects based on composite measures (25) may be entirely due to outcomes that are not important to patients, such as increase in the value of monoclonal protein. Indeed, all trials in our analysis included laboratory-based outcomes in their endpoint definitions for EFS. More important outcomes for patients are clinical outcomes such as end stage organ damage (26) or survival.



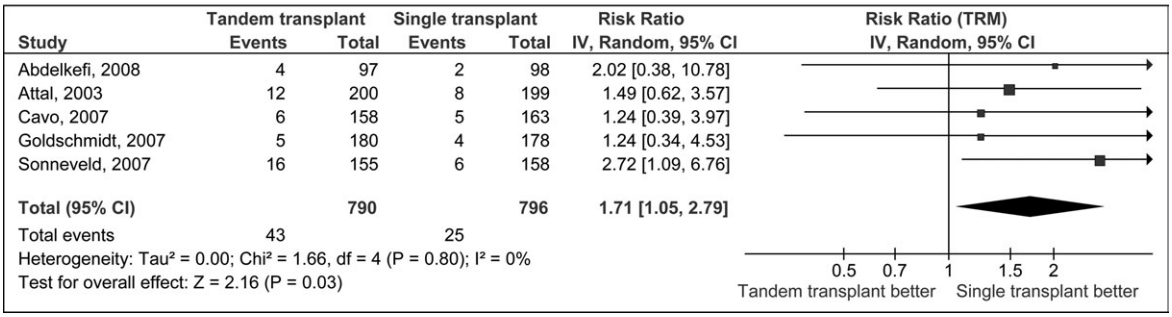


Figure 3. Forest plot of response rate and treatment-related mortality with tandem vs single transplant for myeloma. The summary effect estimate (risk ratio) for individual randomized controlled trials are indicated by **black rectangles** (the size of the rectangle is proportional to the study weight), with the lines representing 95% confidence intervals (CIs). The overall summary effect estimate (risk ratio) and 95% confidence interval are indicated by the **diamond** below.

The first RCT by Attal et al. (6) also indicated that tandem transplant may not benefit all patients equally. The authors concluded that tandem transplant is particularly beneficial in patients younger than 60 years who have had a suboptimal response to a single transplant. Others have argued that other biologic and genomic risk factors such as deletion of the short arm of chromosome 1 (del 1p) (27,28), hypodiploidy (29), t(4;14) (30), and p53 deletion (31) may be even more important in the assessment of therapeutic effects in myeloma. However, none of the studies that compared single and tandem AHCT stratified patients according to these biologic and genomic risk factors that are proposed to affect prognosis of patient with MM. Therefore, it is not known if a benefit in terms of OS may exist in a subgroup of patients with tandem AHCT or if a survival benefit might emerge as strategies to reduce TRM are improved. Collecting individual patient data from all trials to conduct individual patient data meta-analysis may provide additional answers with respect to identification of the subgroup of patients that may benefit from tandem transplant (32). Unfortunately, individual patient data were not available to us.

In conclusion, based on the synthesis of all currently available data, the routine use of tandem transplant in its current form is not justified.

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Notes

A. Kumar and B. Djulbegovic conceptualized and designed the study. They also participated in the collection, analysis, and interpretation of data. A. Kumar and B. Djulbegovic along with A. Glasmacher and M. A. Kharfan-Dabaja jointly drafted the article and critically revised it for intellectual content. There was no funding for this work, which was supported internally by Moffitt Cancer Center. All authors have no financial disclosures to make.

Manuscript received April 30, 2008; revised September 5, 2008; accepted October 30, 2008.