Blood and Marrow
TRANSPLANTATION

REVIEWS

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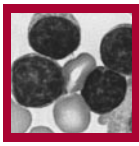
IN THIS ISSUE



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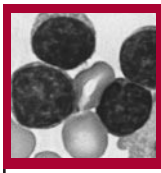
Stem Cell Transplants for Multiple Myeloma: How Do We Know What We Know?

by John R. Wingard, MD, Editor

Evidence-based reviews have assumed important roles in clinical medicine. They offer the clinician comprehensive and timely status reports of what is known about current treatment approaches for a given disease and how well the data support what we think we know. Perhaps equally important is what a review reveals about what we do not know, especially if it challenges some presumptions about what we think we know that are not firmly established. Identification of gaps in knowledge and delineation of research priorities is another important function of the evidence-based review.

The American Society for Blood and Marrow Transplantation (ASBMT) believes that development of a series of evidence-based reviews will address an important need of both the transplant community and a larger non-transplant audience to codify the current state of knowledge of the role of hematopoietic stem cell transplantation (SCT) in the management of various diseases. Using accepted methodology tested for reliability, a panel composed of experts in systematic review procedures, experts in the entire spectrum of treatment options for a given disease topic, SCT experts, a representative of a third-party payer organization, and a patient advocate is convened to prepare the review and interpret the findings for each chosen topic. The first ASBMT review assessed the role of SCT in the management of diffuse large cell B-cell non-Hodgkin's lymphoma and was published in 2001 in *Biology of Blood and Marrow Transplantation* (7:308-331). In this issue, the second review is presented in an abridged form, having been reported in its entirety in the January 2003 issue of *Biology of Blood and Marrow Transplantation*.

As useful as such reviews are, there are limitations. The first is timeliness. In the short interval since preparation of this review, two randomized trials have been presented, adding to our knowledge base and raising new questions. Both studies address issues noted in the review as topics in need of more quality data. One study published by Segeren and colleagues in *Blood* (101:2144-51, 2003) adds new information as to which cytotoxic agents and dose schedules pack more anti-tumor punch and questions whether stem cell support is mandatory for certain cytotoxic regimens which are "dose-dense" but not stem cell ablative. The second, not yet published in a peer-reviewed publication, by Attal and colleagues of the Intergroupe Francophone du Myelome, was presented at the annual meeting of the American Society of Hematology in December 2002 and provided important and provocative new information about the relative merits of a single SCT versus double SCTs. Neither of these two studies invalidates the conclusions of the review, but they make an important point: other randomized trials are in the works and the implication is that this review, and all such reviews, must be periodically revisited to update the evidence and evaluate the impact on recommendations. A second limitation is the lack of high-quality data to address specific important issues in clinical practice. It is fitting that the development of new data, the essence of the first limitation, is ultimately the solution to the second limitation.



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American Society for Blood and Marrow Transplantation

Executive Office
American Society for Blood and Marrow Transplantation
85 West Algonquin Road, Suite 550
Arlington Heights, IL 60005-4425
(847) 427-0224; fax (847) 427-9656
e-mail: mail@asbmt.org

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REVIEW

Blood and Marrow TRANSPLANTATION REVIEWS

This abridgment is presented as a summary of a report that appeared in a recent issue of *Biology of Blood and Marrow Transplantation*. The complete paper can be found in Volume 9, Number 1, pages 4-37.

The Role of Cytotoxic Therapy with Hematopoietic Stem Cell Transplantation in the Therapy of Multiple Myeloma: An Evidence-Based Review

Theresa Hahn,[1] John R. Wingard,[2] Kenneth C. Anderson,[3] William I. Bensinger,[4] James R. Berenson,[5] Greg Brozeit,[6] Joseph R. Carver,[7] Robert A. Kyle,[8] Philip L. McCarthy, Jr.[1]

[1]Roswell Park Cancer Institute, Buffalo, New York; [2]University of Florida College of Medicine, Gainesville, Florida; [3]Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts; [4]The Fred Hutchinson Cancer Research Center, Seattle, Washington; [5]Cedars Sinai Medical Center, Los Angeles, California; [6]International Myeloma Foundation, North Hollywood, California; [7]Abramson Cancer Research Institute, University of Pennsylvania, Philadelphia, Pennsylvania; [8]Mayo Clinic, Rochester, Minnesota, USA

Introduction

The American Society for Blood and Marrow Transplantation (ASBMT) in 1999 began an initiative to sponsor evidence-based reviews of the scientific and medical literature for the use of blood and marrow transplantation in the therapy of selected diseases. The first review in the series evaluating published reports on diffuse large cell B-cell non-Hodgkin's lymphoma was published in 2001 [1]. The following is an edited and abridged version of the second review in which an expert panel assembled and critically evaluated all of the evidence regarding the role of cytotoxic therapy with hematopoietic stem cell transplantation (SCT) in the therapy of multiple myeloma (MM), made treatment recommendations based on the available evidence, and identified needed areas of research [2]. Additional sections that are included in the full-length version of the review but are not presented here include: therapy post-SCT, SCT economic/cost-effectiveness studies, response criteria (methods to detect minimum residual disease), ongoing studies, limitations of this review, and future initiatives.

The published literature was graded in a systematic manner on the quality of design (Table 1) and the strength of the evidence (Table 2). Treatment recommendations subsequently were graded based on the quality and strength of the evidence (Table 3).

Literature Search Methodology

PubMed was systematically searched using the MeSH terms "multiple myeloma" and "transplant." Specific inclusion and exclusion criteria are detailed in the unabridged version of the review.

Qualitative and Quantitative Grading of the Evidence

The hierarchy of evidence, including a grading scheme for the quality and strength of the evidence and strength of each treatment recommendation, was established and published as an editorial policy statement in *Biology of Blood and Marrow Transplantation* [3]. Study design, including sample size, patient selection criteria, duration of follow-up, and treatment plan, also was considered in evaluating the studies.

In this review, stem cell transplantation (SCT) is used as a general term that includes bone marrow transplantation (BMT) and/or peripheral blood stem cell transplantation (PBSCT). De novo therapy refers to only one chemotherapy regimen given before stem cell mobilization and transplantation, and salvage therapy refers to 2 or more chemotherapy regimens given before stem cell mobilization and transplantation. DS indicates Durie-Salmon; TRM, treatment-related mortality; F/U, follow-up; OS, overall survival; EFS, event-free survival; PFS, progression-free survival; FFP, freedom from progression; chemo, standard chemotherapy comparison group; NYR, not yet reached; NS, not stated in article; NC, no comparison given in article.

The treatment recommendations of the expert panel are detailed in Table 4.

Transplantation versus Chemotherapy

Table 5 summarizes the evaluation of the quality and strength of the evidence, patient characteristics, and outcome measures for the reviewed articles, some of which are detailed in this section.

De Novo

Attal et al. compared autologous BMT after 4 to 6 alternating cycles of VMCP (vincristine, melphalan [MEL], cyclophosphamide, and prednisone) and BVAP (carmustine [BCNU], vincristine, adriamycin, and prednisone) (n = 100) versus conventional chemotherapy con-

Table 1. Grading the Quality of the Evidence*

1	Evidence obtained from at least one properly randomized controlled trial
2-1	Evidence obtained from well-designated, controlled trials without randomization
2-2	Evidence obtained from well-designated, cohort or case-controlled analytic studies, preferably from more than one center or research group
2-3	Evidence obtained from multiple timed series with or without the intervention, or from dramatic results in uncontrolled experiments
3	Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees
4	Evidence inadequate owing to problems of methodology, eg, sample size, length or comprehensiveness of follow-up, or conflict in evidence

*Reprinted with permission from Shipp et al. *J Clin Oncol* 17:423-429;1999.

Table 2. Grading the Strength of the Evidence*

1	Experimental therapy significantly better ($P < .05$)
2	Trend in favor of experimental therapy ($P > .05$)
3	No apparent statistical effect
4	Trend favoring control group ($P > .05$)
5	Control group significantly better ($P < .05$)

*Reprinted with permission from Chalmers et al. *Stat Med* 6:733-744;1987.

Table 3. Grading the Strength of the Treatment Recommendation*

1	Effective treatment
2	Marginally effective treatment
3	Not an effective treatment
4	Equivalent treatments (no statistical or clinical difference between therapies)
5	Inadequately evaluated treatment and recommended for comparative study
6	Inadequately evaluated treatment but not recommended for comparative study

*Reprinted with permission from Jones et al. *Biol Blood Marrow Transplant* 6:524-525, 1999.

sisting of 18 alternating cycles of VMCP and BVAP (n = 100) in newly diagnosed, previously untreated stage II or III multiple myeloma (MM) patients aged younger than 65 years [4]. The BMT conditioning regimen consisted of MEL (140 mg/m^2) and total body irradiation (TBI). Recombinant interferon α (IFNa) was administered in 73% of patients in the chemotherapy group starting at cycle 9 until occurrence of relapse (total duration a median of 12 months), and in 70% of the patients in the BMT group starting after hematologic reconstitution (median total duration 11 months). Patients were randomly assigned to 1 treatment arm; 74% of the patients in the BMT group underwent transplantation.

By intent-to-treat, patients in the BMT group had a significantly higher response rate of 38% versus 14% in the chemotherapy group ($P < .001$). At a median follow-up measured from the time of randomization of 37 months in the chemotherapy group and 41 months in the BMT group, the BMT group had significantly longer event-free survival (EFS) ($P = .01$) and overall survival (OS) ($P = .03$) (Figure 1).

Barlogie et al. performed a phase II study of a planned tandem transplantation regimen as part of "total therapy" consisting of vincristine, adriamycin, and dexamethasone (VAD) for 3 cycles, followed by high-dose cyclophosphamide (Cy) and granulocyte-macrophage colony-stimulating factor (GM-CSF); peripheral blood stem cell (PBSC) and/or BM collection; and 1 cycle of etoposide, dexamethasone, cytosine arabinoside, and cisplatinum (EDAP) [5].

For comparison, a sample of historical patients enrolled in Southwest Oncology Group (SWOG) trials 8229 (alternating versus syncopated regimen of VMCP/BVAP) and 8624 (VMCP/BVAP versus VMCPP/BVAPP versus VAD) were pair-matched to the tandem transplantation patients based on age, β-2 microglobulin (B2M), and serum creatinine levels. By intent-to-treat, patients enrolled in the tandem transplantation trial had a significantly higher response rate (≥partial response [PR]) than the pair-matched SWOG trial patients (86% versus 52%; $P = .0001$), longer median duration of EFS (49 versus 22 months; $P = .0001$), and longer median duration of OS (62+ versus 48 months; $P = .01$) (Figure 2).

Lenhoff et al. compared 348 symptomatic, newly diagnosed, previously untreated MM patients aged younger than 60 years treated with high-dose therapy from a prospective population-based study (274 of whom were treated according to a Nordic Myeloma Study Group protocol NMSG #5/94) with 313 his-

Table 4. Summary of Treatment Recommendations Made by the Expert Panel for Multiple Myeloma*

Indication for SCT	Treatment Recommendation†	Highest Level of Evidence‡	Reference No.§	Comments
SCT vs. standard chemotherapy as de novo therapy	1	1	[4]	Ongoing trials may change the recommendation.
SCT vs. standard chemotherapy as salvage therapy	5	2	[11]	There is only 1 non-randomized study that applies.
SCT as de novo vs. salvage therapy	2	1	[14]	These are equivalent in terms of overall survival, however, SCT as de novo is preferred because it may avoid the inconvenience, cost, and risk of myelodysplasia from conventional alkylating agent therapy.
Autologous vs. allogeneic SCT	2	2	[18-25]	Autologous SCT is recommended over a myeloablative allogeneic SCT.
Autologous PBSCT vs. BMT	1	2, 3	[50,51]	PBSCT is preferred based on level 2 evidence regarding engraftment, not survival, outcomes. PBSCT is also the accepted standard based on expert opinion.
Autologous CD34+ selected vs. unselected PBSCT	4	1	[52,53]	
Autologous purged BMT	3	2	[66-69]	
Tandem autologous PBSCT	6	4		A level 1 evidence study has been conducted and will soon be published to address this critical question.
Preferred autologous SCT myeloablative conditioning regimen	1	1	[74]	Melphalan is preferred to melphalan plus TBI based on toxicity not efficacy, however, there is no level 1 evidence comparing melphalan or melphalan plus TBI with other conditioning regimens (eg, busulfan/cyclophosphimide, busulfan/melphalan/thiotepa).
Autologous high-dose sequential regimen	6	4	[93,94]	
Allogeneic BMT vs. PBSCT	6	2	[131]	
Preferred allogeneic SCT myeloablative conditioning regimen	5	4	[132]	There is only 1 feasibility study with a small sample size and no comparison group.
Allogeneic SCT nonmyeloablative regimen	5	4	[133]	There is only 1 feasibility study with a small sample size and no comparison group.
Allogeneic high-dose sequential regimen	6			No evidence.
Autologous SCT followed by allogeneic SCT	5			No evidence published. A study is in progress to address this question.
Maintenance therapy post–autologous SCT with IFNa vs. none	5	4	[139]	Early survival advantage (4-5 y) that is lost over time; problems with study methodology.
Maintenance therapy post–autologous SCT with IFNa vs. other therapies (ie, corticosteroids, thalidomide, or its derivatives)	5			No evidence.

*SCT indicates stem cell transplantation; PBSCT, peripheral blood SCT; BMT, bone marrow transplantation; TBI, total body irradiation; IFNa, interferon α.

†Definitions: See Table 3.

‡Definitions: See Table 1.

§The references listed represent the highest level of evidence used to make the treatment recommendation and are not inclusive of all evidence described in the review.

Table 5. Comparison of Patient Characteristics and Outcomes from Articles on Transplantation versus Chemotherapy*

Reference	Quality of Evidence	Number of Patients in Study	Upper Age Limit (Median), y	DS Stage III	TRM	Median F/U, mo	Strength of Evidence, OS	Median OS, mo	Strength of Evidence, EFS	Median EFS, mo
De novo										
Attal et al. [4]	I	Chemo 100 BMT 100	Chemo 65 (58 mean) BMT 65 (57 mean)	Chemo 77% BMT 72%	Chemo 5% BMT 7%	Chemo 37 BMT 41	I†	Chemo 37.4 BMT NYR	I‡	Chemo 18 BMT 27
Barlogie et al. [5]	2-2	Chemo 116 SCT 123	70	NS	Chemo NS SCT 4%	31	I‡	Chemo 48 SCT NYR 62+	I||	Chemo 22 SCT 49
Lenhoff et al. [6]	2-2	Chemo 274 BMT 274	Chemo 60 (54) PBSCT 60 (51)	Chemo 56% PBSCT 70%	Chemo NS PBSCT 4%	Chemo NS PBSCT 32	I§	Chemo 44 PBSCT NYR	NC	Chemo NS PBSCT 27
Palumbo et al. [7]	2-2	Chemo 71 BMT 71	Chemo 75 (NS) PBSCT 75 (NS)	Chemo 72% PBSCT 75%	Chemo 4% PBSCT 0%	Chemo 39.4 PBSCT 30	I‡	Chemo 48 PBSCT NYR 56+	I§	Chemo 17.7 PBSCT 27
Alexanian et al.[8,9]	2-2	Chemo 68 SCT 50	Chemo 60 (53) SCT 60 (49)	NS	Chemo NS SCT 7%	NS	3	NS	NC	NS
Gianni et al. [10]	2-2	Chemo 19 SCT 13	Chemo 61 (54) SCT 59 (50)	Chemo 42% SCT 92%	Chemo NS SCT 8%	Chemo NS SCT 36	I‡	Chemo 14 SCT 41	NC	NS
Salvage										
Alexanian et al. [11]	2-2	Chemo 79 SCT 49	Chemo 62 (NS) SCT 62 (52)	NS	Chemo NS SCT 14%	NS	3	NS	NC	NS
Mixed disease status— De novo and salvage										
Malpas et al. [12]	2-2	Chemo 120 BMT 36	All patients 84 (62) Chemo 84 (NS) SCT 70 (NS)	71%	Chemo 25% BMT 19.5%	Chemo 63.6 BMT NS	I¶	Chemo 20 BMT 72	NC	NS
Gertz et al [13]	2-1	67	68 (52)	NS	NS	NS	NC	17.2	NC	NS

*Quality of evidence definitions are listed in Table 1; strength of evidence definitions are listed in Table 2. DS indicates Durie-Salmon; TRM, treatment-related mortality; F/U, follow-up; OS, overall survival; EFS, event-free survival; chemo, standard chemotherapy comparison group; BMT, bone marrow transplantation; NYR, not yet reached; NS, not stated in article; SCT, stem cell transplantation (bone marrow and/or peripheral blood; PBSCT, peripheral blood SCT; NC, no comparison given in article.

†$P \leq .05$ and $> .01$.

‡$P \leq .01$ and $> .001$.

§$P \leq .001$ and $> .0001$.

||$P \leq .0001$.

¶$P = .002$ from multivariate, not survival analysis.

torical controls aged younger than 60 years selected from 5 previous population-based Nordic studies of conventional therapy (274 of whom fulfilled the eligibility criteria for the NMSG #5/94 protocol and served as the control group) [6].

By intent-to-treat, OS was significantly longer for the PBSCT group compared with the historical control group (median OS: PBSCT group, not yet reached, control 44 months; risk ratio for controls 1.62; 95% confidence interval [CI] 1.22-2.15; $P = .001$) (Figure 3).

Palumbo et al. treated 71 MM patients aged 55 to 75 years with 2 to 3 cycles of MEL (100 mg/m^2) each followed by PBSC infusion (treated 1993 to 1997) [7]. Patients who underwent PBSCT were compared with a sample of 71 patients (treated 1990 to 1995) matched by age and B2M chosen from a cohort of symptomatic MM patients treated at diagnosis with oral melphalan-prednisolone and who met eligibility criteria for the PBSCT regimen. By intent-to-treat, OS and EFS were significantly longer for the PBSCT group.

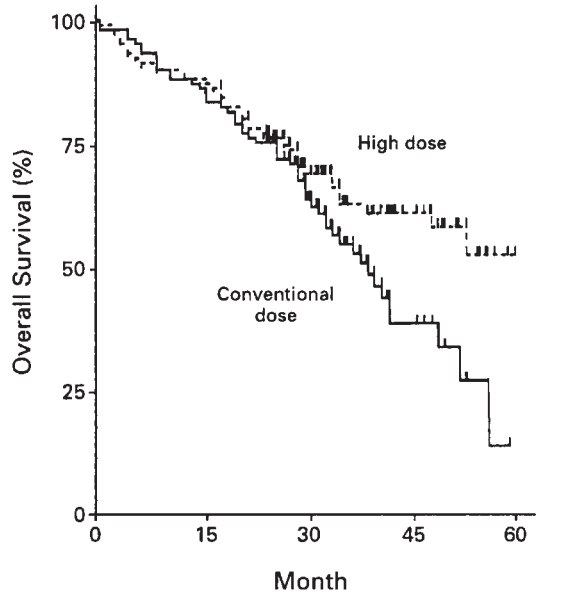

Figure 1. OS according to treatment group. The numbers shown below the time points are probabilities of OS (the percentages of patients surviving) and 95% confidence intervals. Reprinted with permission [4].

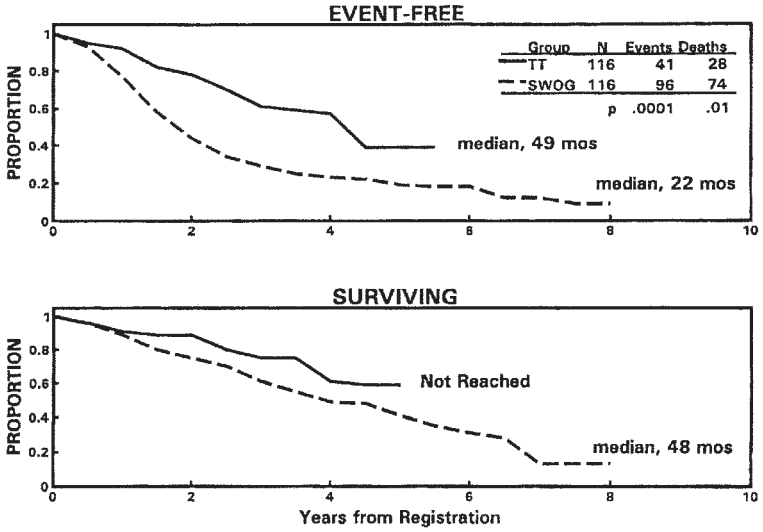

Figure 2. Superior EFS (top) and OS (bottom) among 116 newly diagnosed patients receiving "total therapy" (TT) compared with 116 closely matched "pair mates" receiving standard therapy according to SWOG protocols. The median times of follow-up of living patients on TT and SWOG studies are 31 and 63 months, respectively. Reprinted with permission [5].

Alexanian et al. compared 68 MM patients who received autologous BMT or PBSCT within 1 year after the start of induction chemotherapy with responsive disease (PR or complete response [CR] to induction) with 50 concurrent control patients with similar disease characteristics and prognostic factors who met the eligibility criteria for intensive therapy but did not receive a transplant [8,9]. Median OS of patients who converted from PR to CR after SCT was significantly longer (8.3 years) than those who remained in PR after SCT (5.0 years) and the controls with persistent PR after standard therapy (4.4 years) (P = .03).

Salvage

Alexanian et al. studied 49 MM patients who received VAD plus autologous BMT or PBSCT compared with 79 contemporaneous controls who received VAD but did not meet the eligibility criteria for myeloablative therapy [11]. There was no significant difference between the VAD plus transplantation versus the VAD patients with respect to OS or disease-free survival (DFS).

Mixed Disease Stage (De Novo and Salvage)

Malpas et al. retrospectively compared a cohort of 156 patients treated with conventional chemotherapy (n=120) or autologous BMT (n=36) [12]. OS in the BMT group was prolonged (median 6 years) compared to the conventional chemotherapy group (median 20 months). Multivariate analysis showed increasing age (P = .05) and treatment with conventional chemotherapy (P = .002) were independent risk factors for shorter OS.

Gertz et al. also reported on 118 MM patients who had VAD ×4 cycles as either induction or re-induction (after prior MEL-based chemotherapy) therapy) [13]. A total of 67 patients underwent PBSCT (11 early treatment failures and 56 as a result of progression on or off maintenance therapy) with a median OS after PBSCT of 17.2 months. Median OS from initial MM diagnosis of all 118 transplantation and non-transplantation patients was 58.5 months. There was no comparison of PBSCT as de novo versus salvage therapy.

Timing of Transplantation (De Novo versus Salvage)

Table 6 summarizes the evaluation of the quality and strength of the evidence, patient characteristics, and outcome measures for the reviewed articles, some of which are detailed in this section.

Fermand et al. performed a multicenter prospective randomized trial comparing the optimal timing of autologous PBSCT [14]. At a median follow-up of 58 months, there was no significant difference in OS, however, there was a significant difference in EFS; the early transplantation group's median was 39 months versus the late transplantation group's median of 13 months. The median time without symptoms, treatment, or treatment toxicity (TWiSTT) was 27.8 months for the early transplantation group and 22.3 months for the late transplantation group (Figure 4).

Harousseau et al. treated 97 MM patients with one course of high-dose MEL (120-140 mg/m^2) without stem cell rescue [15]. Patients who achieved at least a PR received an autologous BMT or PBSCT. Patients were

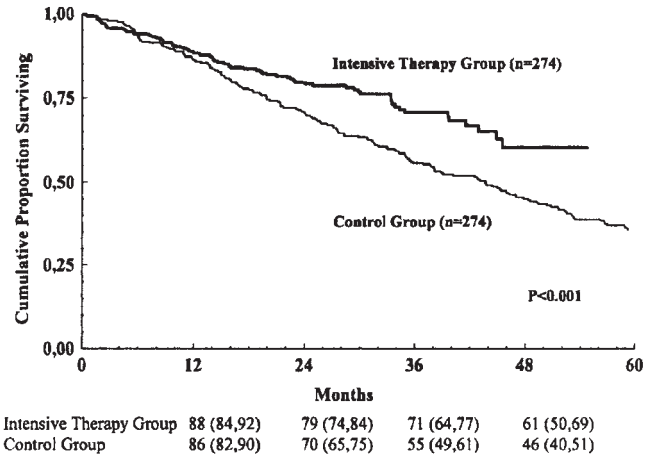

Figure 3. Survival for the intensive therapy group and the control group. The numbers shown below the time points are probabilities of survival in percent, with 95% confidence intervals in brackets. Reprinted with permission [6].

Table 6. Comparison of Patient Characteristics and Outcomes from Articles on Timing of Transplantation (De Novo versus Salvage)

Reference	Quality of Evidence	Number of Patients in Study	Upper Age Limit (Median), y	DS Stage III	TRM	Median F/U, mo	Strength of Evidence, OS	Median OS, mo	Strength of Evidence, EFS	Median EFS, mo
Fermand et al. [14]	1	Early 91 Late 94	Early 56 (48 mean) Late 56 (47 mean)	Early 87% Late 82%	Early 10% Late 14%	58	3	Early NYR 64.6+ Late NYR 64+	1*	Early 39 Late 13
Harousseau et al. [15]	2-1	De novo 53 Salvage 44	De novo 67 (51) Salvage 67 (51)	De novo 94% Salvage 84%	De novo 4% Salvage 10%	32	3	NS	NC	NS
Hawkins et al. [16]	2-2	29	63 (56)	63%	17%	28	3	De novo 47† Salvage 71	NC	NS
Alegre et al. [17]	2-2	259	67 (52)	69%	4%	13	1‡	De novo 45 Salvage 28	NC	NS

*$P < .001$ (calculated by authors, P not stated in article).
†OS from diagnosis.
‡$P \leq .05$ and $> .01$.

divided into 2 groups for analysis: 44 salvage and 53 de novo patients. Those treated as de novo had a longer median OS from a first course of high-dose MEL compared with those given high-dose MEL plus SCT as salvage therapy (37 versus 17 months; $P = .16$). In the 35 patients who received autologous SCT, there was no significant difference in OS or progression-free survival (PFS).

Alegre et al. reported on 259 MM patients from the Spanish Registry (GETH and PETHEMA) treated with autologous PBSCT [17]. Multivariate analysis showed the only independent factors associated with OS and PFS were number of chemotherapy regimens (1 versus other) prior to autologous PBSCT and the disease status prior to PBSCT (CR/PR versus other).

Autologous versus Allogeneic SCT

Table 7 summarizes the evaluation of the quality and strength of the evidence, patient characteristics, and outcome measures for the reviewed articles, some of which are detailed in this section.

Lokhorst et al. prospectively treated 77 newly diagnosed de novo MM patients with VAD ×2 plus intermediate-dose MEL (IDM) (70 mg/m^2) for 2 cycles (n = 62) or IDM for 2 cycles (n = 15) as induction therapy [18]. Patients with at least a PR to induction therapy and an adequate stem cell harvest and who were aged younger than 65 years received autologous PBSCT followed by IFNa maintenance (n = 50). Those who had at least a PR to induction therapy, a human leukocyte antigen (HLA)-identical sibling donor, and were younger than 56 years received an allogeneic BMT (n = 11).There was no statistically significant difference in OS between the autologous and allogeneic transplantation groups; however, there was a trend toward improved EFS in the allogeneic BMT group ($P = .078$).

Seiden et al. performed a prospective study in MM patients of autologous monoclonal antibody–purged BMT (n = 36) or a T-cell depleted allogeneic BMT (n = 22) if an HLA-compatible sibling donor was available [19-21]. Eighty-one percent of autologous BMT patients were alive at the median follow-up of 27 months versus 64% of allogeneic BMT patients alive at a median follow-up of 20 months. Thirty-nine percent of autologous patients were alive and FFP 18 months post-BMT versus 33% of allogeneic patients alive and FFP 30 months post-BMT.

Bjorkstrand et al. retrospectively compared 189 allogeneic BMT patients with HLA-identical sibling donors to 189 autologous PBSCT patients in a matched case-control study using European Group for Blood and Marrow Transplantation (EBMT) Registry data [22]. Median OS was significantly longer in the autologous PBSCT group compared with the allogeneic BMT group (34 versus 18 months; $P = .001$). Median PFS was also longer in the autologous PBSCT group (18 versus 10 months).

Reynolds et al. performed a retrospective single-center comparison of 35 autologous PBSCT patients with 21 historical allogeneic

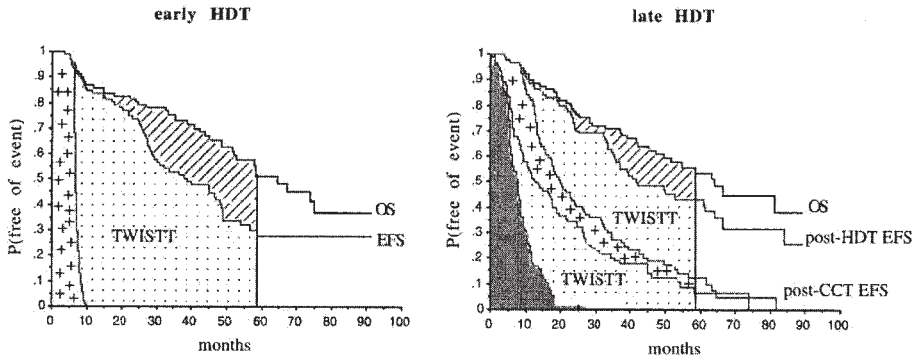

Figure 4. Partitioned Kaplan-Meier survival curves according to treatment group, ie, early HDT group (top) and late HDT group (bottom). Each plot displays the Kaplan-Meier estimations of time to OS, EFS, and time to end of treatment, either conventional chemotherapy (CCT) or transplantation (HDT), since randomization. Note that 2 EFS were considered in the late HDT group (after conventional chemotherapy, "post-CCT," and after transplantation, "post-HDT"). The areas between these curves and the vertical line at 58 months, which corresponds to the median follow-up of the whole cohort, represent estimates of the mean durations between these events, namely treatment duration (either CCT [□] or HDT [+]), time without symptoms and treatment toxicity (TWISTT [■]), and time between relapse and death (▨). All patients were included in the analysis on an intent-to-treat basis. IFN was not taken into account because it was usually maintained only when well-tolerated. Reprinted with permission [14].

Table 7. Comparison of Patient Characteristics and Outcomes from Articles on Autologous versus Allogeneic SCT

Reference	Quality of Evidence	Number of Patients in Study	Upper Age Limit (Median), y	DS Stage III	TRM	Median F/U, mo	Strength of Evidence, OS	Median OS, mo	Strength of Evidence, EFS	Median EFS, mo
Lokhorst et al. [18]	2-1	77	Auto 63 (53) Allo 55 (43)	81% (all patients)	Auto 4% Allo 18%	44 (all patients)	3	Auto NYR Allo NYR	2	Auto 40 Allo NYR
Seiden et al. [19]	2-1	Auto 36 Allo 22	Auto 65 (48) Allo 56 (44)	66% (all patients)	Auto 3% Allo 9%	Auto 27 Allo 20	NC	Auto NYR Allo NS	NC	NS
Bjorkstrand et al. [22]	2-2	Auto 189 Allo 189	Auto 65 (49) Allo 60 (43)	Auto 67% Allo 65%	Auto 13% Allo 41%[a]	Auto 30 Allo 46	1*	Auto 34 Allo 18	NC	NS
Varterasian et al. [23]	2-2	Auto 24 Allo 24	Auto 64 (55) Allo 56 (43)	Auto 21% Allo 18%	Auto 12.5% Allo 25%	Auto 11 Allo 15	3	Auto 33.5 Allo 38.6	3	Auto 16.7 Allo 31
Reynolds et al. [24]	2-2	Auto 35 Allo 21	Auto 68 (55) Allo 56 (48)†	NS	Auto 6% Allo 19%	Auto 15.4 Allo 27.5	3	Auto NYR Allo NYR	NC	NS
Couban et al. [25]	2-2	Auto 40 Allo 22	Auto 57 (45.5) Allo 53 (43)	Auto 62% Allo 50%	Auto 5% Allo 27%	Auto 15 Allo 42	1‡	Auto NYR 48+ Allo 7	NC	NS

*$P \leq .001$ and $>.0001$.
†$P \leq .01$ and $> .001$.
‡$P \leq .05$ and $> .01$.

BMT (n = 6) or PBSCT (n = 15) patients with related donors; both autologous and allogeneic SCT patients were given an identical conditioning regimen: busulfan plus Cy plus TBI (900 cGy) [24]. The Kaplan-Meier probability of disease progression was 11% in the allogeneic group and 64% in the autologous group ($p < .001$). Two-year PFS (60% versus 30%; $P = .19$), 2-year OS (60% versus 42%; $P = .39$), and TRM were higher in the allogeneic group but were not statistically significantly different.

Couban et al. retrospectively compared a cohort of 40 autologous PBSCT and 24 allogeneic BMT or PBSCT patients transplanted for MM at a single center [25]. Three-year PFS was not statistically significantly different between autologous (17%; 95% CI, 0-36.6) and allogeneic (22%; 95% CI, 4-39.6) transplants. Three-year OS was significantly higher in autologous (74%; 95% CI, 52.4-95.6) versus allogeneic (32%; 95% CI, 12.4-51.6) transplant patients.

Autologous SCT

Several studies have demonstrated the feasibility, safety, and efficacy of PBSCT and/or BMT with MEL-based conditioning regimens in previously untreated, newly diagnosed MM patients [26-29], as salvage therapy for relapsed or refractory disease [30-36], and in MM patient populations with mixed disease responses to prior therapy [37-42]. Three studies demonstrated the safety and efficacy of autologous transplantation: 1 study in 17 MM patients aged older than 65 years [43-46]. Four studies have been completed for patients in renal failure [47-49].

Autologous PBSCT versus BMT

Raje et al. compared two sequential phase II studies: the first of patients receiving autologous BMT (n = 26), the second of individuals treated with autologous PBSCT (n = 37) [50]. PBSCT patients recovered platelets significantly faster than BMT patients; however, there were no significant differences with regard to neutrophil engraftment, OS, or PFS.

Harousseau et al. retrospectively compared 81 autologous BMT patients with 51 autologous PBSCT patients from 18 French centers who were treated during a 7-year period [51]. There was no significant difference between the PBSCT and BMT groups regarding CR rate, overall response rate, OS, EFS, or relapse-free survival (RFS). PBSCT patients had a significantly shorter time to neutrophil engraftment but no significant difference in platelet recovery compared with BMT patients.

Autologous $CD34^+$ Selected versus Unselected PBSCT

Table 8 summarizes the evaluation of the quality and strength of the evidence, patient characteristics, and outcome measures for the reviewed articles, some of which are detailed in this section.

Stewart et al. performed a multicenter randomized phase III trial of $CD34^+$ selected (n = 93) versus unselected PBSCT (n = 97) for the treatment of MM [52,53]. There was no difference in the median PFS (Figure 5) or median OS between the $CD34^+$ selected versus unselected treatment arms.

Several feasibility studies of $CD34^+$ selection of PBSC harvests demonstrated its ability to reduce the tumor burden in the products without adversely affecting engraftment kinetics [54-59], and one study demonstrated the feasibility of performing $CD34^+$ selection from multiple cycles of stem cell mobilization and collection [60].

Two studies compared $CD34^+$ selected versus unselected autologous PBSCT patients in prospective, non-randomized clinical trials and found no significant differences in neutrophil or platelet recovery between the 2 groups [61,62]. One study demonstrated that all patients who received a high cell dose had significantly faster neutrophil engraftment and platelet recovery than those who received a low cell dose [63].

One study compared single versus tandem $CD34^+$ selected PBSCT in a non-randomized prospective trial [64] and found no difference in platelet or neutrophil recovery in single or tandem SCT when comparing $CD34^+$ selected versus unselected PBSCT. One case-control study showed a significantly longer time to neutrophil and platelet recoveries in $CD34^+$ selected PBSCT patients but no difference in PFS or OS [65].

Autologous Purged versus Unpurged SCT

Three small studies of fewer than 15 patients each reported the feasibility of different pre-transplant purging techniques, including marrow purged ex vivo with 4-hydroperodxycyclophosphamide [66]; ex vivo immunomagnetic depletion of PBSCT with $CD34^+$ selected products to purge B-lin cells [67] ; and $CD34^+$ selected products followed by CD19 depletion [66].

Barbui et al. randomized 60 newly diagnosed symptomatic MM patients to receive either unmanipulated (n = 31) or purged (n = 29) tan-

Table 8. Comparison of Patient Characteristics and Outcomes from Articles on Autologous CD34+ Selected versus Unselected PBSCT

Reference	Quality of Evidence	Number of Patients in Study	Upper Age Limit (median)	DS Stage III	TRM	Median F/U (mos)	Strength of Evidence	Median d to ANC > 500/mm³	Strength of Evidence†	Median d to Platelets > 20,000/mm³
Stewart et al. [52]	I	Sel 93	Sel 70 (51)	NS	NS	37	3	NS	3	NS
		Unsel 97	Unsel 68 (53)							
Abonour et al. [53]	2-1	18	65 (53)	44%	NS	25	NC	11	NC	15
Lemoli et al. [55]	2-1	23	55 (47.5)	59%	NS	12	3	Sel 10	3	Sel 11
								Unsel 10		Unsel 15
Schiller et al. [58]	2-1	55	69 (52)	55%	11%	33	NC	12	NC	12
Dyson et al. [60]	2-1	34	65 (51)	NS	NS	NS	NC	NS	NC	NS
Patriarca et al. [61]	2-1	Sel 23	Sel 63 (54)	Sel 65%	NS	18	3	Sel 12	3	Sel 21
		Unsel 16	Unsel 62 (55)	Unsel 63%				Unsel 12		Unsel 16
Gupta et al. [62]	2-1	Sel 20	Sel 62 (NS)	NS	0%	23	3	Sel 14	3	Sel 14
		Unsel 16	Unsel 64 (NS)					Unsel 14		Unsel 13
Michallet et al. [63]	2-1	23	65 (55)	77%	9%	15	1	Higher Dose‡ 10	1	Higher Dose 13
								Lower Dose‡ 12		Lower Dose 64
Lemoli et al. [64]	2-1	Single 35	Single 64 (51)	Single 69%	4%	Single 34	Single 3	NC	Single 3	NC
		Tandem 47	Tandem 60 (52)	Tandem 66%		Tandem 28	Tandem 3		Tandem 3	
Gandhi et al. [65]	2-2	Sel 15	Sel 64 (53)	Sel 67%	Sel 13%	Sel 32	1§	Sel 14	1§	Sel 23
		Unsel 15	Unsel 63 (55)	Unsel 60%	Unsel 7%	Unsel 57		Unsel 11		Unsel 14

*Strength of evidence comparing neutrophil engraftment.
†Strength of evidence comparing platelet engraftment.
‡Higher dose: CD34+Thy1+ >0.8 × 10^6 cells/kg, lower dose: CD34+Thy1+ <0.8 × 10^6 cells/kg.
§$P \leq .05$ and $> .01$.

dem PBSCT [69]. There was no difference in the time to neutrophil or platelet recovery, discharge from hospital, or transfusion requirements between the purged and unpurged PBSCTs. At a median follow-up of 23 months, the 3-year EFS rate was 72% in the purged and 40% in the unpurged PBSCT group ($P = .05$). The 3-year OS rate was 83% for the purged and 83% for the unpurged PBSCT groups.

Autologous Tandem versus Single SCT

Table 9 summarizes the evaluation of the quality and strength of the evidence, patient characteristics, and outcome measures for the reviewed articles, some of which are detailed in this section.

In Barlogie et al. [5] additional patients were accrued in the tandem transplantation regimen and follow-up of the original patients was updated [70]. By intent-to-treat, 5-year OS and EFS rates for tandem transplant patients were 58% and 42%, respectively.

Vesole et al. compared patients with advanced and refractory MM who received MEL with no stem cell rescue (MEL100) versus MEL plus TBI or thiotepa plus TBI and autologous BMT (MEL140) versus MEL with autologous BM plus PBSCT as a tandem transplantation (MEL200) [71]. A multivariate regression analysis of favorable factors for EFS found that low B2M, MEL200, primary unresponsive disease, and age 50 years or younger were statistically significant. B2M, MEL200, ≤12 months from diagnosis, and age 50 years or younger were statistically significant predictors of prolonged OS.

Siegel et al. compared tandem transplantation in a sample of 49 patients with advanced stage MM aged 65 years or older to pair-mates younger than 65 years matched on 5 prognostic factors [72]. Median durations of EFS and OS and TRM were not significantly different between the younger and older groups.

Autologous SCT Conditioning Regimens

Table 10 summarizes the evaluation of the quality and strength of the evidence, patient characteristics, and outcome measures for the

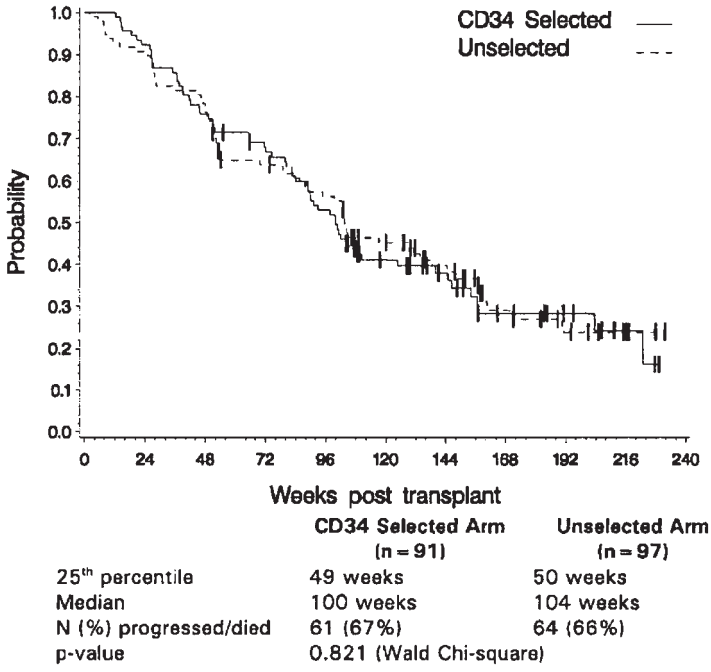

Figure 5. Kaplan-Meier probability of progression-free survival of 188 patients on an intent-to-treat basis. Reprinted with permission [51].

Table 9. Comparison of Patient Characteristics and Outcomes from Articles on Autologous Tandem versus Single SCT

Reference	Quality of Evidence	Number of Patients in Study	Upper Age Limit (Median), y	DS Stage III	TRM	Median F/U, mo	Strength of Evidence, OS	Median OS, mo	Strength of Evidence, EFS	Median EFS, mo
Barlogie et al. [70]	2-1	Enrolled 231 2 BMTs 165	71 (51)	53%	5%	NS	NC	68	NC	43
Vesole et al. [71]	2-2	MEL100 47 MEL140 21 MEL200 67	NS	NS	MEL100 19% MEL140 24% MEL200 1%	NS	1*	MEL100 7 MEL140 16 MEL200 NYR 43+	1†	MEL100 5 MEL140 8 MEL200 21
Siegel et al. [72]	2-2	<65 49 ≥65 49	<65 64 (52) ≥65 76 (67)	<65 49% ≥65 59%	<65 2% ≥65 8%	NS (minimum 18 months)	3	<65 57.6 ≥65 39.6	3	<65 33.6 ≥65 18
Bjorkstrand et al. [73]	2-1	1 BMT 15 2 BMTs 11	57 (48)	73%	7%	21 (after first transplantation)	NC	NYR 19+	NC	NS

*P = .001.
†P = .0001.

Table 10. Comparison of Patient Characteristics and Outcomes from Articles on Autologous SCT Conditioning Regimens*

Reference	Quality of Evidence	Conditioning Regimen Dose (No, of Patients)	Upper Age Limit (Median), y	DS Stage III	TRM	Median F/U, mo	Strength of Evidence, OS	Median OS, mo	Strength of Evidence, EFS	Median EFS, mo
Moreau et al. [74]	1	Mel 200 (142)	65 (61)	75%	0%	20.5	1†	NYR	3	20.5
		vs. Mel 140	65 (60)	79%	4%	20n		43		21
		TBI 800 (140)								
Tribalto et al. [75]	2-1	Bu 16 Mel 60 (39)	60 (49)	48%n	3%	55	NC	57	NC	21
Meloni et al. [77]	2-1	Ida Bu Mel 60 (28)	69 (55)	57%	0%	20	NC	NS	NC	NS
Mansi et al. [78]	2-1	Bu 8 or 16 (15)	64 (52)	NS	20%	7	NC	8	NC	NS
Long et al. [79]	2-1	VCTBI (12) or CBV (22)	65 (49)	47%	6%	38	NC	NS	NC	NS
Shimoni et al. [81]	2-1	TtBuC (120)	67 (48)	57%	13%	29	NC	NS	NC	NS
Alegre et al. [83]	2-1	Bu 12Mel 140 (24)	60 (48)	79%	4%	20	NC	NS	NC	NS
Ventura et al. [84]	2-1	CBV (11)	NS	NS	9%	NS	NC	12+	NC	NS
Barlogie et al. [85]	2-2	Mel 100 (46)	NS	NS	28%	108	1‡	4.8	1§	2.4
		vs. Mel 100+GM (24)			17%			21.6		6
		vs. Mel 140ABMT (8)			13%			8.4		4.8
		vs. Mel 140TBIABMT (37)			11%			33.6		15.6
		vs. TtTBIABMT (18)			0%	7.2			22.8	
Bensinger et al. [86]	2-1	Bu 14-16 C 120-174 (18)	66 (51)	43%	28%	31.2	NC	NS	NC	NS
		vs. Bu 14 C 120 TBI 600-1050 (36)			14%					
		vs. Bu 12 Mel 100 Tt500 (9)			11%					
Goldschmidt et al. [87]	2-1	Mel 200 (50)	65 (54)	80%	0%	16	NC	NS	NC	NS
		vs. Mel140TBI (50)	60 (50)	72%n	4%					
Chen et al. [89]	2-2	VMelTBI (94)	NS	NS	14%	11.8	NC	NYR 58+	NC	NS
		BuCy (32)			3%					
Lahuerta et al. [90]	2-2	Mel 200 (472)	55‖	68%	4%	NS	3	46	3	22
		Mel 140TBI (135)	49‖	68%	8%			39		20
		BuMel (186)	50‖	66%	6%			57		30
		BuC (28)	53‖	66%	0%			39		23
Desikan et al. [92]	2-2	Second SCT: Mel 200 (43)	NS	NS	0%	NS	1¶	76	1#	61
		Mel 200Cy 120 (19)			0%			39		27
		Mel 140TBI 1125 (24)			8%			25		15

*Mel indicates melphalan; Bu, busulfan; Ida, idarubicin; V, etoposide; C, cyclophosphamide; B, carmustine; Tt, thiotepa; GM, granulocyte-macrophage colony-stimulating factor; ABMT, autologous BMT, Second SCT, conditioning regimen for first transplantation was Mel 200 whereas the second transplantation regimen varied as indicated. Other abbreviation definitions are listed in the Table 5 footnote.
†P = .05 comparing the rate of 45-mo OS: 65.8% (MEL) vs. 45.5% (MEL plus TBI).
‡P = .0004.
§P = .0001.
‖ Means not medians, upper limit not stated.
¶P = .003 comparing Mel200 vs. other.
#P < .0001 comparing Mel200 vs. other.

Table 11. Summary of Prognostic Factors for OS, EFS, CR Rate, and Favorable Engraftment in Patients Treated with Autologous SCT

Reference No.	Factors
Independent laboratory indicators of prolonged OS	
[95]	Non-plasmablastic morphology
[4,71,97,98]	Low β-2 microglobulin
[104]	Low C-reactive protein
[97,99]	Immunoglobulin G isotype
[100]	High glomerular filtration rate
[105]	Early absolute lymphocyte count recovery
[106]	No deletion of chromosome 13q14
[107]	Normal cytogenetics
Independent clinical indicators of prolonged OS	
[17,97,98,101-104]	Disease status at time of SCT (in CR or with chemotherapy-responsive disease)
[15-17]	SCT as de novo therapy (vs. salvage)
[8,96]	Achievement of CR post-SCT
[22,25]	Autologous SCT (vs. allogeneic)
[102]	Melphalan-containing conditioning regimen
[102]	Male gender
[102]	Stage I disease at diagnosis
[12]	Younger age
Clinical and laboratory indicators that are not significant predictors of OS or EFS	
[108]	Number of reinfused plasma cells (EFS)
[109]	Light chain associated amyloidosis (OS/EFS)
[110]	Magnetic resonance imaging pattern 1 mo before and after SCT (OS)
Clinical and laboratory indicators in tandem PBSCT	
	Higher CR rate
[111]	Low β-2 microglobulin
[111]	Low C-reactive protein
[111]	No chromosome 13 abnormalities
[111]	Less than 1 y of prior chemotherapy
	Prolonged OS and EFS
[70,72,112-114]	Absence of chromosomal abnormalities
[70,72,112-114]	Low β-2 microglobulin
[113]	Low C-reactive protein
[113]	Attainment of CR
[113]	Two PBSCTs given within a 6-month period
[112,114]	Shorter duration of chemotherapy before first PBSCT
Clinical and laboratory indicators for favorable/rapid engraftment after SCT	
	Platelet engraftment
[115]	Cy⁺G-CSF (vs. G-CSF alone) as SC mobilization regimen
[115]	No prior oral MEL exposure
	Neutrophil and platelet engraftment
[116]	No prior MEL exposure
[116]	>2 × 10^6 $CD34^+$ cells/kg infused
[117]	Duration of prior chemotherapy
[117]	Number of $CD34^+$ cells infused
[117]	≤24 months of prior chemotherapy needs ≥2.0 × 10^6 $CD34^+$ cells/kg
[117]	>24 months of prior chemotherapy needs 5.0 × 10^6 $CD34^+$ cells/kg

reviewed articles. Seven studies have described the feasibility and efficacy of novel conditioning regimens [75-84]; 5 studies have retrospectively compared SCT regimens for single transplantations [85-91], and 1 study for tandem transplantation [92].

Autologous High-Dose Sequential Therapy

Palumbo et al. investigated an intensified regimen in 68 patients newly diagnosed with MM treated with dexamethasone, adriamycin, and vincristine (DAV) ×3 cycles for induction therapy [93,94]. By intent-to-treat, CR was induced in 27% of patients; CR plus PR was induced in 85%. TRM was 3%; median EFS was 35.6 months.

Prognostic Factors for OS, EFS, CR Rate, and Favorable Engraftment in Patients Treated with Autologous SCT

Table 11 summarizes the evaluation of the quality and strength of the evidence, patient characteristics, and outcome measures for the reviewed articles.

Other observations included the following: plasma cell labeling index was significantly higher in patients with abnormal cytogenetics [108,118]; prolonged prior therapy with alkylating agents (more than 1 prior cycle of chemotherapy before SC mobilization) was associated with developing myelodysplastic syndrome (MDS) posttransplantation [119]; elevated plasma cell light chain ratio (LCR) in the first 60 days post-SCT most likely indicated residual tumor and not early relapse, however, an elevated LCR >90 days post-SCT significantly correlated with disease progression [120]; failure to achieve CR (as measured by electrophoresis and immunofixation) after SCT was independently predicted by prior therapy with 2 or more chemotherapy regimens, nonresponsive disease at time of SCT, and TBI-containing conditioning regimen [121].

Syngeneic SCT

Only two small studies of patients treated with BMT from syngeneic donors were available for review. One, a retrospective case-matched analysis, compared MM patients treated with syngeneic BMT to autologous SCT and allogeneic SCT patients. [122] A second described patients with MM given salvage therapy with a BMT from syngeneic donors [123]. No treatment recommendations were made due to insufficient evidence. are available

Allogeneic SCT

Table 12 summarizes the evaluation of the quality and strength of the evidence, patient characteristics, and outcome measures for the reviewed articles.

Prognostic Factors for PFS, OS, and EFS in Patients Treated with Allogeneic SCT

There is no evidence or insufficient evidence to make recommendations on the fol-

Table 12. Comparison of Patient Characteristics and Outcomes from Articles on Allogeneic SCT

Reference	Quality of Evidence	Number of Patients in Study	Upper Age Limit (Median), y	DS Stage III	TRM	Median F/U, mo	Strength of Evidence, OS*	Median OS, mo	Strength of Evidence, EFS*	Median EFS, mo
Barlogie et al. [70]	2-1	Enrolled 231	71 (51)	53%	5%	NS	NC	68	NC	43
Gahrton et al. [122]	2-2	90	55 (42)	68%	NS	79 (mean)	NC	26	NC	NS
LeBlanc et al. [128]	2-1	37	53 (47)	68%	16%*	40	NC	NS	NC	NS
Reece et al. [129]	2-1	26	54 (43)	81%	19%†	14	NC	NS	NC	NS
Majolino et al. [130]	2-1	10	53 (45)	80%	20%*	16.5	NC	NYR 14+	NC	NS

*TRM by day 120 post-SCT.
†TRM by day 100 post-SCT.

lowing issues related to allogeneic SCT (Table 13):

- Allogeneic SCT nonmyeloablative conditioning regimen [124-129].
- Allogeneic PBSCT versus BMT [131].
- Preferred allogeneic SCT myeloablative conditioning regimen [132-133].
- Allogeneic high-dose sequential regimen.

Therapy Post-SCT

Due to insufficient evidence, no recommendation was made of a preferred maintenance therapy posttransplantation, including maintenance interferon, donor lymphocyte infusion and second transplant for relapse. The question was recommended for comparative study.

Economic/Cost-Effectiveness Studies

Several studies have examined the cost-effectiveness of stem cell transplantation with varying results, depending on the patient population studied, the range of direct and/or indirect costs included, and the stated endpoints of the analysis. These are detailed in the unabridged version of this review.

Response Criteria (Methods to Detect Minimum Residual Disease)

Various techniques to measure biochemical or molecular tumor markers have been examined for their ability to detect minimum residual disease in apheresis products, BM harvests, or in MM patients pre- and posttransplantation and to predict prognosis. There is not sufficient evidence, however, to recommend a preferred method to detect minimum residual disease.

Ongoing Studies

Several studies have been published in abstract form only, have recently been completed, or are currently accruing patients that address critical issues that will affect treatment recommendations based on the evidence available at the time of this review. The final analyses of mature data from these studies will provide additional evidence that may change and/or add to the conclusions and recommendations of the authors.

Limitations of this Evidence-Based Literature Review

There are limitations to any evidence-based review of the published literature. The criteria for this review included only data from peer-reviewed manuscripts published since 1980. Unpublished data and data published only in abstract form were excluded. Another limitation is the review's reliance on published data rather than individual patient data. Although it was not the objective of this review to perform a meta-analysis of individual patient data, such an analysis is warranted in the future to further clarify the results of studies and address questions that remain unanswered.

Discussion

Several studies have been published in abstract form only, were recently completed, or are currently accruing patients but address critical issues that will affect the treatment recommendations made above [137-141].

The panel recommends studies of post-response therapy to improve the quality of the response and extend survival as the most important area of needed research.

In addition to the topics covered, we reviewed the evidence for PBSC mobilization regimens, and timing of PBSC collections for SCT and vaccine therapy post-autologous SCT. The panel concluded that there was not adequate evidence to make meaningful recommendations in these areas. The panel noted that although expert opinion has set an upper age limit of 70 years for autologous SCT, the decision for transplantation in the elderly population should be made on a case-by-case basis.

The authors recommend methodology standardization, including study design, analytical tests, and response criteria. Multicenter randomized phase III comparative trials with large enrollments and high statistical power are required in the United States to advance the field more constructively than single institution phase II trials with one treatment arm. We advocate prompt reporting of mature data in full manuscript format.

The treatment recommendations of this panel are based on the results of well-planned, scientifically sound, peer-reviewed clinical trials. All of today's current therapy for cancer is the result of the randomized clinical trial process. It is currently estimated that less than 5% of adults eligible to participate in cancer clinical trials actually enroll in a trial. The authors acknowledge the importance of third

Table 13. Summary of Prognostic Factors for PFS, OS, and EFS in Patients Treated with Allogeneic SCT

Reference No.	Factors
Statistically significant independent indicators of prolonged PFS	
[126]	Chemotherapy-sensitive disease at time of SCT
[127]	<Stage III disease
Statistically significant independent indicators of prolonged OS	
[124,134]	Achievement of CR post-SCT
[124]	Grade I acute GVHD
[134]	<Grade III acute GVHD
[135]	Chemotherapy-sensitive disease at time of SCT
[135]	Low B-2 microglobulin (<2.5 g/L)
[135]	Less than 1 y between diagnosis and SCT
[128]	Fewer cycles of chemotherapy prior to allogeneic SCT
Statistically significant independent indicators of prolonged EFS	
[131]	Chemotherapy-sensitive disease at time of SCT
[135]	No prior autologous SCT
[135]	Creatinine clearance > 100 mL/min

party payers in removing one barrier to participation in clinical trials by providing insurance coverage for the routine costs of care for patients enrolled in cancer clinical trials. We urge all carriers to extend benefits for participation in cancer clinical trials that is at least consistent with the scope of coverage defined by the Center for Medicare and Medicaid Services in the September 19, 2000 regulations to answer the critical treatment questions, not only for MM, but also for other malignant diseases.

Acknowledgments

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References

1. Hahn T et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of diffuse large cell B-cell non-Hodgkin's lymphoma: an evidence based review. *Biol Blood Marrow Transplant*. 2001;7:308-331.
2. Hahn T 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.
3. Jones R et al. Policy statement regarding the methodology of evidence-based reviews in evaluating the role of blood and marrow transplantation in the therapy of selected diseases. *Biol Blood Marrow Transplant*. 1999;6:524-525.
4. Attal M 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. Barlogie B et al. Superiority of tandem autologous transplantation over standard therapy for previously untreated multiple myeloma. *Blood*. 1997;89:789-793.
6. Lenhoff S 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 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. Alexanian R et al. Impact of complete remission with intensive therapy in patients with responsive multiple myeloma. *Bone Marrow Transplant*. 2001;27:1037-1043.
9. Alexanian R et al. Early myeloablative therapy for multiple myeloma. *Blood*. 1994;84:4278-4282.
10. Gianni AM 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.
11. Alexanian R et al. Limited value of myeloablative therapy for late multiple myeloma. *Blood*. 1994;83:512-516.
12. Malpas JS et al. Myeloma during a decade: clinical experience in a single centre. *Ann Oncol*. 1995;6:11-18.
13. Gertz MA et al. Early harvest and late transplantation as an effective therapeutic strategy in multiple myeloma. *Bone Marrow Transplant*. 1999;23:221-226.
14. Fermand JP 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.
15. Harousseau JL et al. Double-intensive therapy in high-risk multiple myeloma. *Blood*. 1992;79:2827-2833.
16. Hawkins T et al. An incremental response to high-dose therapy in multiple myeloma. *Bone Marrow Transplant*. 1996;17: 929-935.
17. Alegre A et al. Autologous peripheral blood stem cell transplantation for multiple myeloma: a report of 259 cases from the Spanish Registry. Spanish Registry for Transplant in MM (Grupo Espanol de Trasplante Hematopoyetico-GETH) and PETHEMA. *Bone Marrow Transplant*. 1998;21:133-140.
18. Lokhorst HM et al. Induction therapy with vincristine, adriamycin, dexamethasone (VAD) and intermediate-dose melphalan (IDM) followed by autologous or allogeneic stem cell transplantation in newly diagnosed multiple myeloma. *Bone Marrow Transplant*. 1999; 23:317-322.
19. Seiden MV et al. Monoclonal antibody-purged bone marrow transplantation therapy for multiple myeloma. *Leuk Lymphoma*. 1995;17:87-93.
20. Anderson, KC et al. Monoclonal antibody-purged bone marrow transplantation therapy for multiple myeloma. *Blood*. 1993;82:2568-2576.
21. Anderson KC et al. Monoclonal antibody-purged autologous bone marrow transplantation therapy for multiple myeloma. *Blood*. 1991;77:712-720.
22. Bjorkstrand BB et al. Allogeneic bone marrow transplantation versus autologous stem cell transplantation in multiple myeloma: a retrospective case-matched study from the European Group for Blood and Marrow Transplantation. *Blood*. 1996;88:4711-4718.
23. Varterasian M et al. Transplantation in patients with multiple myeloma: a multicenter comparative analysis of peripheral blood stem cell and allogeneic transplant. *Am J Clin Oncol*. 1997;20:462-466.
24. Reynolds C et al. Allogeneic stem cell transplantation reduces disease progression compared to autologous transplantation in patients with multiple myeloma. *Bone Marrow Transplant*. 2001;27:801-807.
25. Couban S et al. Autologous and allogeneic transplantation for multiple myeloma at a single centre. *Bone Marrow Transplant*. 1997;19:783-789.
26. Gore ME et al. Intensive treatment of multiple myeloma and criteria for complete remission [see comments]. *Lancet*. 1989;2:879-882.
27. Attal M et al. Intensive combined therapy for previously untreated aggressive myeloma. *Blood*. 1992;79: 1130-1136.
28. Cunningham D et al. High-dose melphalan and autologous bone marrow transplantation as consolidation in previously untreated myeloma. *J Clin Oncol*. 1994. 12;759-63.
29. Hovenga S et al. Autologous stem cell transplantation in multiple myeloma after VAD and EDAP courses: a high incidence of oligoclonal serum Igs post transplantation. *Bone Marrow Transplant*. 2000;25:723-728.
30. Barlogie B et al. High-dose melphalan with autologous bone marrow transplantation for multiple myeloma. *Blood*. 1986;67:1298-1301.
31. Barlogie B et al. High-dose chemoradiotherapy and autologous bone marrow transplantation for resistant multiple myeloma. *Blood*. 1987;70:869-872.
32. Dimopoulos MA et al. Intensive chemotherapy with blood progenitor transplantation for primary resistant multiple myeloma. *Br J Haematol*. 1994;87:730-734.
33. Gertz MA et al. Refractory and relapsing multiple myeloma treated by blood stem cell transplantation. *Am J Med Sci*. 1995;309:152-161.
34. Rajkumar SV et al. Autologous stem cell transplantation for relapsed and primary refractory myeloma. *Bone Marrow Transplant*. 1999;23:1267-1272.
35. Vesole DH et al. High-dose melphalan with autotransplantation for refractory multiple myeloma: results of a Southwest Oncology Group phase II trial. *J Clin Oncol*. 1999;17: 2173-2179.
36. Mansi JL et al. Repeat administration of high dose melphalan in relapsed myeloma. *Br J Cancer*. 1993;68: 983-987.
37. Fermand JP et al. Treatment of aggressive multiple myeloma by high-dose chemotherapy and total body irradiation followed by blood stem cells autologous graft. *Blood*. 1989;73:20-23.
38. Fermand JP et al. High-dose chemoradiotherapy and autologous blood stem cell transplantation in multiple myeloma: results of a phase II trial involving 63 patients. *Blood*. 1993; 82:2005-2009.
39. Jagannath S et al. Low-risk intensive therapy for multiple myeloma with combined autologous bone marrow and blood stem cell support. *Blood*. 1992;80: 1666-1672.
40. Marit G et al. Autologous peripheral-blood progenitor-cell support following high- dose chemotherapy or chemoradiotherapy in patients with high-risk multiple myeloma. *J Clin Oncol*. 1996;14:1306-1313.
41. Williams CD et al. Autologous bone marrow transplantation in multiple myeloma: a single centre experience of 23 patients. *Leuk Lymphoma*. 1994;15:273-279.
42. Mahendra P et al. Autografting for multiple myeloma: a 5-year experience at a single institution. *Bone Marrow Transplant*. 1995;16:759-763.
43. Sirohi B et al. The role of autologous transplantation in patients with multiple myeloma aged 65 years and over. *Bone Marrow Transplant*. 2000;25:533-539.
44. Badros A et al. Autologous stem cell transplantation in elderly multiple myeloma patients over the age of 70 years. *Br J Haematol*. 2001;114:600-607.
45. Aslan T et al. Patients with multiple myeloma may safely undergo autologous transplantation despite ongoing RSV infection and no ribavirin therapy. *Bone Marrow Transplant*. 1999;24: 505-509.
46. Badros A et al. Results of autologous stem cell transplant in multiple myeloma patients with renal failure. *Br J Haematol*. 2001;114:822-829.
47. Ballester OF et al. High-dose chemotherapy and autologous peripheral blood stem cell transplantation in patients with multiple myeloma and renal insufficiency. *Bone Marrow Transplant*. 1997;20:653-656.
48. Tosi P et al. Safety of autologous hematopoietic stem cell transplantation in patients with multiple myeloma and chronic renal failure. *Leukemia*. 2000;14: 1310-1313.
49. Tricot G et al. Safety of autotransplants with high-dose melphalan in renal failure: a pharmacokinetic and toxicity study. *Clin Cancer Res*. 1996;2:947-952.
50. Raje N et al. Comparison of marrow vs blood-

derived stem cells for autografting in previously untreated multiple myeloma. *Br J Cancer.* 1997;75:1684-1689.
51. Harousseau JL et al. Comparison of autologous bone marrow transplantation and peripheral blood stem cell transplantation after first remission induction treatment in multiple myeloma. *Bone Marrow Transplant.* 1995;15:963-969.
52. Stewart AK et al. Purging of autologous peripheral-blood stem cells using CD34 selection does not improve overall or progression-free survival after high-dose chemotherapy for multiple myeloma: results of a multicenter randomized controlled trial. *J Clin Oncol.* 2001;19:3771-3779.
53. Vescio R et al. Multicenter phase III trial to evaluate CD34(+) selected versus unselected autologous peripheral blood progenitor cell transplantation in multiple myeloma [see comments]. *Blood.* 1999;93:1858-1868.
54. Abonour R et al. Autologous transplantation of mobilized peripheral blood CD34+ cells selected by immunomagnetic procedures in patients with multiple myeloma. *Bone Marrow Transplant.* 1998;22:957-963.
55. Lemoli RM et al. Concomitant mobilization of plasma cells and hematopoietic progenitors into peripheral blood of multiple myeloma patients: positive selection and transplantation of enriched CD34+ cells to remove circulating tumor cells. *Blood.* 1996;87:1625-1634.
56. Lemoli RM et al. Selection and transplantation of autologous hematopoietic CD34+ cells for patients with multiple myeloma. *Leuk Lymphoma.* 1997;26(suppl 1):1-11.
57. Lemoli RM, Cavo M, Fortuna A. Concomitant mobilization of plasma cells and hematopoietic progenitors into peripheral blood of patients with multiple myeloma. *J Hematother.* 1996;5:339-349.
58. Schiller G et al. Autologous CD34-selected blood progenitor cell transplants for patients with advanced multiple myeloma [see comments]. *Bone Marrow Transplant.* 1998;21: 141-145.
59. Schiller G et al. Transplantation of CD34+ peripheral blood progenitor cells after high- dose chemotherapy for patients with advanced multiple myeloma. *Blood.* 1995;86:390-397.
60. Dyson PG et al. CD34+ selection of autologous peripheral blood stem cells for transplantation following sequential cycles of high-dose therapy and mobilization in multiple myeloma. *Bone Marrow Transplant.* 2000;25: 1175-1184.
61. Patriarca, F et al. High-dose therapy in multiple myeloma: effect of positive selection of CD34+ peripheral blood stem cells on hematologic engraftment and clinical outcome. *Haematologica.* 2000;85:269-274.
62. Gupta D et al. CD34+-selected peripheral blood progenitor cell transplantation in patients with multiple myeloma: tumour cell contamination and outcome. *Br J Haematol.* 1999; 104:166-177.
63. Michallet M et al. Transplantation with selected autologous peripheral blood CD34+Thy1+ hematopoietic stem cells (HSCs) in multiple myeloma: impact of HSC dose on engraftment, safety, and immune reconstitution. *Exp Hematol.* 2000; 28:858-870.
64. Lemoli RM et al. Engraftment, clinical, and molecular follow-up of patients with multiple myeloma who were reinfused with highly purified CD34+ cells to support single or tandem high-dose chemotherapy. *Blood.* 2000;95:2234-2239.
65. Gandhi M et al. A comparison of CD34+ cell selected and unselected autologous peripheral blood stem cell transplantation for multiple myeloma: a case controlled analysis. *Bone Marrow Transplant.* 1999;24: 369-375.
66. Reece DE et al. Treatment of multiple myeloma with intensive chemotherapy followed by autologous BMT using marrow purged with 4-hydroperoxycyclophosphamide. *Bone Marrow Transplant.* 1993;11:139-146.
67. Lemoli RM et al. Selection and transplantation of autologous CD34+ B-lineage negative cells in advanced-phase multiple myeloma patients: a pilot study. *Br J Haematol.* 1999;107: 419-428.
68. Rasmussen T et al. Efficacy and safety of CD34-selected and CD19-depleted autografting in multiple myeloma patients: a pilot study. *Exp Hematol.* 2002;30:82-88.
69. Barbui A et al. Negative selection of peripheral blood stem cells to support a tandem autologous transplantation programme in multiple myeloma. *Br J Haematol.* 2002;116: 202-210.
70. Barlogie B. et al. Total therapy with tandem transplants for newly diagnosed multiple myeloma. *Blood.* 1999;93:55-65.
71. Vesole DH et al. High-dose therapy for refractory multiple myeloma: improved prognosis with better supportive care and double transplants. *Blood.* 1994;84: 950-956.
72. Siegel DS et al. Age is not a prognostic variable with autotransplants for multiple myeloma. *Blood.* 1999; 93:51-54.
73. Bjorkstrand B et al. Double high-dose chemoradiotherapy with autologous stem cell transplantation can induce molecular remissions in multiple myeloma. *Bone Marrow Transplant.* 1995;15:367-371.
74. Moreau P 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 Myélome 9505 randomized trial. *Blood.* 2002;99:731-735.
75. Tribalto M et al. Autologous peripheral blood stem cell transplantation as first line treatment of multiple myeloma: an Italian Multicenter Study. *Haematologica.* 2000;85:52-58.
76. Tribalto M et al. Treatment of multiple myeloma with autologous blood stem cell transplantation. Preliminary results of an Italian multicentric pilot study. *Int J Artif Organs.* 1993;16(suppl 5):51-56.
77. Meloni G et al. High-dose idarubicine, busulphan and melphalan as conditioning for autologous blood stem cell transplantation in multiple myeloma. A feasibility study. *Bone Marrow Transplant.* 2000;26:1045-1049.
78. Mansi J et al. High-dose busulfan in patients with myeloma. *J Clin Oncol.* 1992;10:1569-1573.
79. Long GD et al. High dose etoposide-based myeloablative therapy followed by autologous blood progenitor cell rescue in the treatment of multiple myeloma. *Cancer.* 1996;78: 2502-2509.
80. Dimopoulos MA et al. Thiotepa, busulfan, and cyclophosphamide: a new preparative regimen for autologous marrow or blood stem cell transplantation in high-risk multiple myeloma. *Blood.* 1993;82:2324-2328.
81. Shimoni A et al. Thiotepa, busulfan, cyclophosphamide (TBC) and autologous hematopoietic transplantation: an intensive regimen for the treatment of multiple myeloma. *Bone Marrow Transplant.* 2001;27: 821-828.
82. Dimopoulos MA et al. Intensive sequential therapy for VAD-resistant multiple myeloma. *Leuk Lymphoma.* 1994;13: 479-484.
83. Alegre A et al. Busulfan and melphalan as conditioning regimen for autologous peripheral blood stem cell transplantation in multiple myeloma. *Br J Haematol.* 1995;91:380-386.
84. Ventura GJ et al. High dose cyclophosphamide, BCNU and VP-16 with autologous blood stem cell support for refractory multiple myeloma. *Bone Marrow Transplant.* 1990; 5:265-268.
85. Barlogie B et al. Long-term follow-up after high-dose therapy for high-risk multiple myeloma. *Bone Marrow Transplant.* 1998;21:1101-1107.
86. Bensinger WI et al. High-dose therapy followed by autologous hematopoietic stem-cell infusion for patients with multiple myeloma. *J Clin Oncol.* 1996;14:1447-1456.
87. Goldschmidt H et al. High-dose therapy with peripheral blood progenitor cell transplantation in multiple myeloma [see comments]. *Ann Oncol.* 1997;8:243-246.
88. Goldschmidt H et al. Peripheral blood progenitor cell transplantation in multiple myeloma following high-dose melphalan-based therapy. *Recent Results Cancer Res.* 1998;144: 27-35.
89. Chen CI et al. Radiation-associated pneumonitis following autologous stem cell transplantation: predictive factors, disease characteristics and treatment outcomes. *Bone Marrow Transplant.* 2001;27:177-182.
90. Lahuerta JJ et al. Myeloablative treatments for multiple myeloma: update of a comparative study of different regimens used in patients from the Spanish Registry for Transplantation in Multiple Myeloma. *Leuk Lymphoma.* 2002;43:67-74.
91. Lahuerta JJ et al. Conditioning regimens in autologous stem cell transplantation for multiple myeloma: a comparative study of efficacy and toxicity from the Spanish Registry for Transplantation in Multiple Myeloma. *Br J Haematol.* 2000;109: 138-147.
92. Desikan KR et al. Melphalan plus total body irradiation (MEL-TBI) or cyclophosphamide (MEL-CY) as a conditioning regimen with second autotransplant in responding patients with myeloma is inferior compared to historical controls receiving tandem transplants with melphalan alone. *Bone Marrow Transplant.* 2000;25:483-487.
93. Palumbo A et al. Dose-intensive melphalan with stem cell support (CM regimen) is effective and well tolerated in elderly myeloma patients. *Haematologica.* 2000; 85:508-513.
94. Palumbo A et al. Multicyclic, dose-intensive chemotherapy supported by hemopoietic progenitors in refractory myeloma patients. *Bone Marrow Transplant.* 1997;19:23-29.
95. Rajkumar SV et al. Plasmablastic morphology is an independent predictor of poor survival after autologous stem-cell transplantation for multiple myeloma. *J Clin Oncol.* 1999;17: 1551-1557.
96. Rajkumar SV et al. Beta2-microglobulin and bone marrow plasma cell involvement predict complete responders among patients undergoing blood cell transplantation for myeloma. *Bone Marrow Transplant.* 1999; 23:1261-1266.
97. Jagannath S et al. Autologous bone marrow transplantation in multiple myeloma: identification of prognostic factors. *Blood.* 1990;76:1860-1866.
98. Majolino I et al Autologous transplantation in multiple myeloma: a GITMO retrospective analysis on 290 patients. Gruppo Italiano Trapianti di Midollo Osseo. Haematologica, 1999;84:844-852.
99. Sirohi, B et al. Comparison of new patients with Bence-Jones, IgG and IgA myeloma receiving sequential therapy: the need to regard these immunologic subtypes as separate disease entities with specific prognostic criteria. *Bone Marrow Transplant.* 2001;28:29-37.
100. Sirohi B et al. Glomerular filtration rate prior to high-dose melphalan 200 mg/m^2 as a surrogate marker of outcome in patients with myeloma. *Br J Cancer.* 2001;85:325-332.

101. Moreau P et al. Melphalan 220 mg/m2 followed by peripheral blood stem cell transplantation in 27 patients with advanced multiple myeloma. *Bone Marrow Transplant.* 1999;23: 1003-1006.
102. Bjorkstrand B et al. Prognostic factors in autologous stem cell transplantation for multiple myeloma: an EBMT Registry Study. European Group for Bone Marrow Transplantation. *Leuk Lymphoma.* 1994;15:265-272.
103. Dumontet C et al. Reduced progression-free survival in elderly patients receiving intensification with autologous peripheral blood stem cell reinfusion for multiple myeloma. *Bone Marrow Transplant.* 1998;21:1037-1041.
104. Gertz MA et al. Delayed stem cell transplantation for the management of relapsed or refractory multiple myeloma. *Bone Marrow Transplant.* 2000;26:45-50.
105. Porrata LF et al. Early lymphocyte recovery predicts superior survival after autologous hematopoietic stem cell transplantation in multiple myeloma or non-Hodgkins lymphoma. *Blood.* 2001;98:579-585.
106. Worel N et al. Deletion of chromosome 13q14 detected by fluorescence in situ hybridization has prognostic impact on survival after high-dose therapy in patients with multiple myeloma. *Ann Hematol.* 2001;80: 345-348.
107. Rajkumar S et al. Abnormal cytogenetics predict poor survival after high-dose therapy and autologous blood cell transplantation in multiple myeloma. *Bone Marrow Transplant.* 1999; 24:497-503.
108. Boccadoro M et al. Multiple myeloma: the number of reinfused plasma cells does not influence outcome of patients treated with intensified chemotherapy and PBPC support. *Bone Marrow Transplant.* 2000;25:25-29.
109. Desikan KR et al. Incidence and impact of light chain associated (AL) amyloidosis on the prognosis of patients with multiple myeloma treated with autologous transplantation. *Leuk Lymphoma.* 1997;27:315-319.
110. Lecouvet FE et al. Bone marrow transplantation in patients with multiple myeloma: prognostic significance of MR imaging. *AJR Am J Roentgenol.* 2001;176:91-96.
111. Desikan R et al. Results of high-dose therapy for 1000 patients with multiple myeloma: durable complete remissions and superior survival in the absence of chromosome 13 abnormalities. *Blood.* 2000;95:4008-4010.
112. Tricot G et al. Unique role of cytogenetics in the prognosis of patients with myeloma receiving high-dose therapy and autotransplants. *J Clin Oncol.* 1997;15: 2659-2666.
113. Vesole DH et al. Autotransplants in multiple myeloma: what have we learned? *Blood.* 1996;88:838-847.
114. Tricot G et al. Predicting long-term (≥5 years) event-free survival in multiple myeloma patients following planned tandem autotransplants. *Br J Haematol.* 2002;116:211-217.
115. Gertz MA et al. Factors influencing platelet recovery after blood cell transplantation in multiple myeloma. *Bone Marrow Transplant.* 1997;20:375-380.
116. Millar BC et al. Role of CD34+ cells in engraftment after high-dose melphalan in multiple myeloma patients given peripheral blood stem cell rescue. *Bone Marrow Transplant.* 1996;18: 871-878.
117. Tricot G et al. Peripheral blood stem cell transplants for multiple myeloma: identification of favorable variables for rapid engraftment in 225 patients. *Blood.* 1995;85:588-596.
118. Rajkumar SV et al. Cytogenetic abnormalities correlate with the plasma cell labeling index and extent of bone marrow involvement in myeloma. *Cancer Genet Cytogenet.* 1999;113: 73-77.
119. Govindarajan R et al. Preceding standard therapy is the likely cause of MDS after autotransplants for multiple myeloma. *Br J Haematol.* 1996;95:349-353.
120. Maia DM et al. The significance of light chain-restricted bone marrow plasma cells after peripheral blood stem cell transplantation for multiple myeloma. *Am J Clin Pathol.* 1997;107: 643-652.
121. Lahuerta JJ et al. Remission status defined by immunofixation vs. electrophoresis after autologous transplantation has a major impact on the outcome of multiple myeloma patients. *Br J Haematol.* 2000;109:438-446.
122. Gahrton G et al. Syngeneic transplantation in multiple myeloma—a case-matched comparison with autologous and allogeneic transplantation. European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant.* 1999;24: 741-745.
123. Bensinger WI et al. Syngeneic marrow transplantation in patients with multiple myeloma. *Bone Marrow Transplant.* 1996;18:527-531.
124. Gahrton G et al. Allogeneic bone marrow transplantation in multiple myeloma. European Group for Bone Marrow Transplantation [see comments]. *N Engl J Med.* 1991;325: 1267-1273.
125. Gahrton G et al. Allogeneic bone marrow transplantation in patients with multiple myeloma. *Eur J Haematol.* 1989; 43(suppl 51):182-185.
126. Gahrton G et al. Allogeneic bone marrow transplantation in 24 patients with multiple myeloma reported to the EBMT registry. *Hematol Oncol.* 1988;6:181-186.
127. Gahrton G et al. Bone marrow transplantation in multiple myeloma: report from the European Cooperative Group for Bone Marrow Transplantation. *Blood.* 1987;69: 1262-1264.
128. LeBlanc R et al. Allogeneic transplantation for multiple myeloma: further evidence for a GVHD-associated graft-versus-myeloma effect. *Bone Marrow Transplant.* 2001;28:841-848.
129. Reece DE et al. Treatment of myeloma using intensive therapy and allogeneic bone marrow transplantation. *Bone Marrow Transplant.* 1995;15:117-123.
130. Majolino I et al. Allogeneic transplantation of unmanipulated peripheral blood stem cells in patients with multiple myeloma. *Bone Marrow Transplant.* 1998;22: 449-455.
131. Gahrton G et al. Progress in allogeneic bone marrow and peripheral blood stem cell transplantation for multiple myeloma: a comparison between transplants performed 1983-93 and 1994-98 at European Group for Blood and Marrow Transplantation centres. *Br J Haematol.* 2001;113:209-216.
132. Cavo M et al. High-dose busulfan and cyclophosphamide are an effective conditioning regimen for allogeneic bone marrow transplantation in chemosensitive multiple myeloma. *Bone Marrow Transplant.* 1998;22:27-32.
133. Badros A et al. Improved outcome of allogeneic transplantation in high-risk multiple myeloma patients after nonmyeloablative conditioning. *J Clin Oncol.* 2002; 20:1295-1303.
134. Gahrton G et al. Prognostic factors in allogeneic bone marrow transplantation for multiple myeloma [see comments]. *J Clin Oncol.* 1995;13:1312-1322.
135. Bensinger WI et al. Allogeneic marrow transplantation for multiple myeloma: an analysis of risk factors on outcome. *Blood.* 1996;88:2787-2793.
136. Kulkarni S et al. Impact of previous high-dose therapy on outcome after allografting for multiple myeloma. *Bone Marrow Transplant.* 1999;23:675-680.
137. Maloney D et al. Combining an allogeneic graft-vs-myeloma effect with high-dose autologous stem cell rescue in the treatment of multiple myeloma. *Blood.* 2001;98:434a. Abstract 1822.
138. Fermand JP et al. In single versus tandem high dose therapy (HDT) supported with autologous blood stem cell (ABSC) transplantation using unselected or CD34 enriched ABSC: preliminary results of a two by two randomized trial in 230 young patients with multiple myeloma (MM). *Blood.* 2001;98:815a. Abstract 3387.
139. Segeren C et al. Myeloablative treatment following intensified chemotherapy in untreated multiple myeloma: a prospective, randomized phase III study. *Blood.* 2001;98:815a. Abstract 3388.
140. Blade J et al. High-dose therapy autotransplantation/intensification vs continued conventional chemotherapy in multiple myeloma patients responding to initial treatment chemotherapy. Results of a prospective randomized trial from the Spanish Cooperative Group PETHEMA. *Blood.* 2001;98: 815a. Abstract 3386.
141. Kropff M et al. Randomized trial comparing an intensified therapy (HD-IMC) with a standard high-dose therapy (HD-M) for multiple myeloma. *Blood.* 2000;96: 797a. Abstract 3444.

Online Tutorial Helps Explain New CPT Codes

A major overhaul of the CPT Codes for hematopoietic stem cell collection and transplantation took effect in January. The new codes replaced the previous limited number of codes that over the years had become outdated and too vague to adequately define stem cell transplantation procedures.

An online tutorial, posted on the ASBMT Web site at ***www.asbmt.org***, provides transplanters and administrators details on the changes, including codes that have been added, revised, and deleted.

The new codes and their relative values are based on complexity of the procedure, the amount of physician involvement, time required, intellectual effort needed, health risk to the patient, and potential liability.

Although the new codes are now available for submitting claims to private payers, the Centers for Medicare and Medicaid Services (CMS) does not yet recognize and accept all of the new cell processing codes. Efforts to attain CMS recognition of the cell processing codes are continuing by the ASBMT and ASH committees.

Standardized RFI Forms Now Available on the Web

Reporting of transplant center statistics and treatment outcomes to third-party payers took a major step toward simplification and uniformity with the introduction in January of the first standardized Request for Information (RFI) form.

Nearly two years in development, the new ASBMT forms are the product of extensive input from BMT clinicians and administrators, as well as critique by payer representatives.

The RFIs can be viewed, printed, and downloaded as interactive forms from the ASBMT Web site at ***www.asbmt.org***.

"There has been a long-time concern in the BMT community about the wide variability and inconsistency of RFI survey instruments," said Patrick Stiff, MD, chair of the ASBMT Committee on Standardized Outcomes Reporting and RFIs. "The new standardized RFIs will give BMT centers and payers the potential of a single set of forms for reporting data on program administration and treatment outcomes.

"The objective for the forms has been more accurate reporting and reduced administrative burdens and costs," he said.

The standardized forms are designed for reporting data on both allogeneic and autologous hematopoietic stem cell transplantation for adult and pediatric patients. Several payer companies have already begun using the new forms in requesting information from transplant centers.

"We are asking national companies to disseminate the forms to their member plans to speed adoption at the community level," Dr. Stiff said. "Judging by the acceptance so far, we are expecting the standardized RFIs to be widely used."

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