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Allogeneic Peripheral Blood Stem-Cell Compared With Bone Marrow Transplantation in the Management of Hematologic Malignancies: An Individual Patient Data Meta-Analysis of Nine Randomized Trials

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Abstract

Purpose—Considerable uncertainty exists regarding relative effects of allogeneic peripheral blood stem cells transplantation (PBSCT) versus bone marrow transplantation (BMT) on outcomes of patients with hematologic malignancies.

Patients and Methods—To provide the totality of research evidence related to the effects of PBSCT versus BMT, we conducted an individual-patient data meta-analysis using data from nine randomized trials enrolling 1,111 adult patients.

Results—Compared with BMT, PBSCT led to faster neutrophil (odds ratio [OR] = 0.31; 95% CI, 0.25 to 0.38; $P < .00001$) and platelet engraftment (OR = 0.52; 95% CI, 0.44 to 0.61; $P < .00001$). PBSCT was associated with a significant increase in the development of grade 3-4 acute graft-versus-host disease (GVHD; OR = 1.39; 95% CI, 1.03 to 1.88) and extensive (47% *v* 31% at 3 years; OR = 1.89; 95% CI, 1.47 to 2.42; $P < .000001$) and overall chronic GVHD (68% *v* 52% at 3 years; OR = 1.92; 95% CI, 1.47 to 2.49; $P < .000001$), but not grade 2-4 acute GVHD (54% *v* 53%; $P = .49$). PBSCT was associated with a decrease in relapse (21% *v* 27% at 3 years; OR = 0.71; 95% CI, 0.54 to 0.93; $P = .01$) in both late-stage– (33% *v* 51% at 3 years; OR = 0.59; 95% CI, 0.38 to 0.93; $P = .02$) and early-stage– disease patients (16% *v* 20% at 3 years; OR = 0.69; 95% CI, 0.49 to 0.98; $P = .04$). Nonrelapse mortality was not different between groups. Overall and disease-free survival were only statistically significantly improved in patients with late-stage disease (overall survival: 46% *v* 31% at 3 years; OR = 0.64; 95% CI, 0.46 to 0.90; $P = .01$; disease-free survival: 41% *v* 27% at 3 years; OR = 0.63 95% CI, 0.45 to 0.87; $P = .01$).

Conclusion—PBSCT is associated with a decreased relapse rate in hematologic malignancies and improvement in overall and disease-free survival in patients with late-stage disease. PBSCT is also associated with a significant risk of extensive chronic GVHD.

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INTRODUCTION

While peripheral blood stem cells (PBSC) are used almost exclusively in autologous transplantation, recent surveys indicate that PBSC are used in 50% to 60% of allogeneic stem-cell transplants.[1] Thus, large variation in practice and considerable uncertainty exists with respect to the relative effects of allogeneic PBSC transplantation (PBSCT) versus bone marrow transplantation (BMT) on the outcomes of patients with hematologic malignancies. In order to address this question, several randomized controlled trials have been conducted. Despite several well designed and executed clinical trials, taken individually, most of these trials were too small to draw definitive conclusions, and not surprisingly, substantial controversy still remains regarding the impact on the occurrence of graft-versus-host disease (GVHD), mortality, disease control, and other important clinical outcomes.[2-5]

This controversy is typical in health care research and demonstrates the need for a systematic review to assemble the totality of relevant research evidence to determine the relative merits of new interventions and therapies. The “gold-standard” for combining evidence from existing randomized trials is an individual patient data meta-analysis (IPD-MA) in which updated data on each and every participant from each and every relevant trial are centrally collected, processed, and analyzed.[6,7] Here, we report the first IPD-MA examining the differences in the outcomes between human leukocyte antigen (HLA) –matched, related allogeneic PBSCT and BMT as therapy for hematologic malignancies.

PATIENTS AND METHODS

Recommended procedures for the meta-analysis based on the individual patient data were followed.[6-8] Randomized controlled trials (RCTs) in which adult patients with hematologic malignancies and HLA-matched sibling donors were randomly assigned to PBSCT and BMT were eligible for the analysis. We performed an extensive search of a number of computerized databases (MEDLINE, EMBASE, LILACS, CANCERLIT, The Cochrane Library) and the abstracts of meetings of the American Society of Hematology, European Hematology Association, American Society of Clinical Oncology, IBMTR (International Bone Marrow Transplant Registry), and EBMT (European Group for Blood and Marrow Transplantation) from 1990 to 2002. Experts in oncology and hematology were asked about ongoing or closed studies that had not yet been published. Details of the search strategy were published as a Cochrane protocol.[9] Periodic searches were subsequently performed with the cutoff for the trial identification and data collection as of August 2003. Once eligible trials were identified, their principal investigators were contacted, and a central database was formed. Demographic data (patient and donor age and sex, diagnosis and disease status at the time of transplantation, cytomegalovirus serology); information regarding the transplantation procedure (date of random assignment and of transplantation, allocated treatment [PBSCT or BMT], conditioning regimen used [total-body irradiation– based *v* non–total-body irradiation– based], graft processing and manipulation, number of CD3 cells/kg and C34 cells/kg transplanted, GVHD prophylaxis, use of post-transplantation growth factors); and details of the trial design, including randomization methodology, were collected. The following outcome data were collected for each patient: time to neutrophil and platelet engraftment, date of relapse or disease progression; date of onset and grade of acute GVHD and chronic GVHD, and the date of last follow-up or death. Cause of death was distinguished between relapse-related and non–relapse-related.

Extensive data checking was performed using the methods described previously.[6,7,10,11] Data were checked for obvious inconsistencies and were amended as necessary through intensive correspondence with the responsible principal investigators. Raw data were also compared with aggregate data in available publications. Detailed checks for any imbalance in accrual

between two randomized arms, follow-up and length of follow-ups, and the numbers in subgroups were also performed.

All comparisons were based on an intention-to-treat principle. Individual patient data allowed calculation of required statistics using the exact dates of events, which is more statistically reliable and clinically informative than basing the calculations on proportions alive at a particular point in time.[6,11,12] Briefly, the number of events observed (O) in the PBSCT arm of each trial is compared with the number expected (E) if the events in that trial had been equally distributed between the PBSCT and BMT arms. The difference between these numbers, O - E, and its variance yields the log-rank test for each trial. The sum of the statistics is first produced for each trial. The individual log-rank statistics from each trial were then combined to give an overall estimate of the effect of PBSCT versus BMT on the outcomes of interest. The important point here is that the analysis is not done by pooling all patients in one mega-analysis, but rather pooling was done by combining individual log-rank statistics to obtain the overall log-rank statistics for all trials, which are then used to calculate reductions of overall odds of death or other outcomes of interest. This means that the methods employed in our analysis preserve the original randomization in each trial since they do **not** involve any analyses in which patients in one trial are directly compared with patients in another trial.[6,7,11,12] The results are expressed in such a way that the annual odds of event of interest of 0.75 might equivalently be described as an odds ratio, a hazard ratio of 0.75, an odds reduction of 25%, or a 25% reduction in the event rate.[6,12] Assumption-free methods were used.[6,12] All *P* values are two-tailed.

Heterogeneity (ie, variability or differences between studies in the estimates of effects) was also assessed. We evaluated methodological heterogeneity (differences in study design), clinical heterogeneity (differences between studies in key characteristics of the participants, interventions, or outcome measures; Table 1), and statistical heterogeneity.[8] Formal tests for heterogeneity were performed to investigate whether the effect size might be different among the studies/subgroups (ie, if observed variability in results is greater than that expected to occur by chance).[6] All subgroup analyses were defined a priori.

The main end points analyzed were: overall survival, relapse/progression, GVHD, disease-free survival, death in remission and engraftment. Time was calculated from the date of randomization; in the case of acute and chronic GVHD it was calculated from the date of randomization, date of transplant, and day +100 after the transplantation (in case of chronic GVHD). Since the results did not change appreciably, only the latter analyses are shown. Disease-free survival was defined as time to death or relapse, whichever occurred first. Due to small numbers, the analyses according to disease types were not reliable and were, therefore, supplemented with the analysis according to disease prognostic features. A uniform consensus among all trialists was achieved to separate patients into those with “early-stage” (chronic myelogenous leukemia [CML] in first chronic phase, acute myeloid leukemia [AML] and acute lymphoblastic leukemia [ALL] in first complete remission, and refractory anemia/refractory anemia with ringed sideroblasts subtypes of myelodysplastic syndromes [MDS]) and “late-stage” disease (CML in second chronic phase, accelerated phase or blast crisis; AML or ALL, refractory or in ≥ second remission; refractory anemia with excess blasts or in transformation subtypes of MDS, multiple myeloma, Hodgkin’s disease, non-Hodgkin’s lymphoma, and idiopathic myelofibrosis). (The patients with Hodgkin’s disease and non-Hodgkin’s lymphoma were considered to have unfavorable, “late stage” disease since they were heavily pretreated and presented with advanced features of their disease, usually after receiving autologous transplant first.)

The study was approved by the University of South Florida institutional review board (IRB # 100701).

RESULTS

Trials and Patients

We identified 12 RCTs enrolling 1,318 patients with various hematologic malignancies that compared HLA-matched, related allogeneic PBSCT with BMT (Sahovic E et al, "Allogeneic peripheral blood vs. bone marrow transplant in hematologic malignancies: A randomized trial," personal communication, 2002),[13-23] 11 of which have been published at the time of the analysis (Table 1). The requirements of the QUOROM (Quality of Reports of Meta-analyses of Randomized Controlled Trials) statement were followed.[24] Individual patient data were provided on 1,288 patients from 11 trials (Table 1).

Table 1 presents the characteristics of all trials and patients considered in our analysis. Two trials differed substantially in the design from the rest: the Dutch trial[20] included T-cell depletion of the grafts, while the Australian trial[13] examined PBSCT versus granulocyte colony-stimulating factor primed BMT. It was unanimously agreed by all trialists that these trials should not be included in the pooled analysis. While some differences existed among the other trials, it was felt that all trials tested similar interventions for similar conditions under similar circumstances to allow pooling of their data in this meta-analysis.[6] Data from one trial (N = 29) were not provided, but were extracted from the published report of this trial when possible.[18] Inclusion or exclusion of the data from this trial did not materially alter the results. Thus, data on 1,111 patients from nine trials were included in the final analysis. Overall, treatment groups appeared well balanced according to the most important prognostic features (ie, age, sex, disease type, and so on; Table 1). Figure 1 shows the patient distribution according to the prognostic features. Median duration of follow-up of patients included in our analysis was 2.7 years (range, 0 to 8.6 years).

The main results of the analysis are summarized in the forest plot shown in Figure 2.

Engraftment

There was a highly significant reduction in the number of days to reach the absolute neutrophil count of 0.5×10^9/L in the patients receiving PBSCT, and a platelet count greater than 20×10^9/L. Median time to neutrophil and platelet engraftment was 14 *v* 21 days ($\chi^2 = 97.59$; $P < .00001$) and 14 *v* 22 days ($\chi^2 = 53.3$; $P < .00001$) in the PBSCT and BMT arms, respectively.

Acute GVHD

There was no difference in overall incidence in acute GVHD grades 1-4 between the two treatment groups (54% *v* 53%; $P = .49$). Forty percent of the patients developed grade 2-4 acute GVHD with no significant increase in the rate after PBSCT (odds ratio [OR] = 1.14; 95% CI, 0.93 to 1.4; $P = .2$; Fig 3A).However, grades 3-4 acute GVHD occurred more often after PBSCT (by approximately 6% at 100 days [$\chi^2 = 4.58$; $P = .03$]; OR = 1.39 [95% CI, 1.03 to 1.88]; Fig 3B).

Chronic GVHD

There was a highly significant increase in the odds of developing of both extensive stage (OR = 1.89; 95% CI, 1.47 to 2.42; $P < .00001$) and overall (any stage; OR = 1.92; 95% CI, 1.47 to 2.49; $P < .00001$) chronic GVHD in patients treated with PBSCT. At 3 years, 47% and 68% of patients treated with PBSCT developed extensive or any stage chronic GHVD versus 31% and 52%, after BMT, respectively (Figs 4A and B). At 5 years, the corresponding figures for PBSCT versus BMT were 51% *v* 35% for extensive stage chronic GVHD and 73% *v* 56% for any stage, respectively. The results remained virtually the same regardless of the start date of calculation of chronic GVHD (ie, whether it was from the date of randomization, date of transplant or day +100 after transplantation, respectively).

Relapse, Relapse Mortality, and Nonrelapse Mortality

Relapsed or progression rate at 3 and 5 years in PBSCT arm was 21% and 24% *v* 27% and 32% in the patients treated with BMT, respectively (OR = 0.71; 95% CI, 0.54 to 0.93; *P* = .01; Fig 5). The difference in the early-disease group was 16% *v* 20% at 3 years, and 16% *v* 25% at 5 years, respectively (OR = 0.69; 95% CI, 0.49 to 0.98; *P* = .04). In the late-disease group, the difference was 33% *v* 51% at 3 years and 44% *v* 58% at 5 years, respectively (OR = 0.59; 95% CI, 0.38 to 0.93; *P* = .02; Fig 6), but the test for interaction between the two groups was not significant (*P* = .6).

Eleven percent and 14% of patients died due to relapse/progression of disease in the PBSCT group, versus 16% and 18% in the BMT arm at 3 and 5 years, respectively ($\chi^2 = 5.51$; *P* = .02). Relapse-related mortality followed the same pattern, indicating that once disease relapsed/progressed, a salvage treatment may, on average, not be effective (Fig 7A).

Approximately 30% of patients died in both groups due to nonrelapse causes (OR = 0.99; 95% CI, 0.79 to 1.25; *P* = 1.0). As expected, most deaths due to treatment occurred early after transplantation (Fig 7B).

Disease-Free Survival

Overall, allogeneic PBSCT was associated with a statistically significant improvement in disease-free survival over BMT (OR = 0.80; 95% CI, 0.67 to 0.97; *P* = .02; 59% *v* 53% at 3 years and 54% *v* 47% at 5 years, respectively; Fig 8). This difference was more pronounced in patients with late disease (41% *v* 27% at 3 years; and 32% *v* 21% at 5 years, respectively; OR = 0.63 95% CI, 0.45 to 0.87; *P* = .01) than in patients with early disease (OR = 0.85; 95% CI, 0.67 to 1.08); *P* = .2; Fig 9). However, a test for interaction between the two groups was not significant (*P* = .1).

Survival

There was no statistically significant difference in overall survival between PBSCT and BMT (OR = 0.87; 95% CI, 0.72 to 1.06; *P* = .17; Figs 10 and 11). However, PBSCT was associated with a higher 5-year overall survival probability in the subpopulation with late disease (46% *v* 31% at 3 years, and 39% *v* 29% at 5 years, respectively; OR = 0.64; 95% CI, 0.46 to 0.90; *P* = .01) but not in patients with early disease (65% *v* 64%; OR = 0.97; 95% CI, 0.75 to 1.25); *P* = .8; Fig 12). Test for interaction was borderline statistically significant (*P* = .05).

Statistical heterogeneity of treatment effect between trials was noted only for relapse outcome ($\chi^2 = 14.6$; *P* = .04) and neutrophil ($\chi^2 = 32.2$; *P* = .000008) and platelet engraftment ($\chi^2 = 33.6$; *P* = .00005).

Subgroup Analyses

To elucidate if the effect of the type of transplantation differed among different disease groups, we performed a number of subgroup analyses. Briefly, the most consistent effect is seen in CML, in which PBSCT was associated with improvement in relapse in all patients (OR = 0.34; 95% CI, 0.2 to 0.58), and improvement in disease-free and overall survival in patients with late-stage disease (OR = 0.28 [95% CI, 0.11 to 0.73] for disease-free survival, and OR = 0.31 [95% CI, 0.12 to 0.80] for overall survival, respectively). PBSCT also led to improvement in disease-free survival (OR = 0.39; 95% CI, 0.21 to 0.72) and overall survival (OR = 0.45; 95% CI, 0.24 to 0.85) in AML patients with late-stage disease. Due to small number of patients (Fig 1), we could not confirm or refute superiority of PBSCT versus BMT in other disease categories.

DISCUSSION

According to international registry data, approximately half of transplant physicians prefer allogeneic PBSCT over BMT.[1,25] To address the question of which source of hematopoietic stem cells might be preferable, we conducted the first IPD-MA of prospective randomized trials comparing transplantation of HLA-matched, related allogeneic PBSCT and BMT in patients with hematologic malignancies. It is important to realize that our results and conclusions apply only to matched sibling myeloablative allogeneic transplantation and not to the role of nonmyeloablative transplantation or alternative donor strategies.

Our analysis should be interpreted within the context of the extreme logistical difficulties associated with performing large randomized trials in allogeneic transplantation. Because hematologic diseases are rare and transplant numbers are relatively low even in large centers, most trials chose to enroll patients with a variety of hematologic malignancies. However, by pooling all existing data, we were able to increase the power of the analysis and provide the most definitive evidence to date.

Our analysis demonstrated that stem cell source is not statistically significant in its effect on overall survival. However, PBSCT is associated with an increase in both survival and disease-free survival in advanced-stage disease. PBSCT is also associated with significantly more rapid neutrophil and platelet engraftment, a reduced relapse rate and an increase in the risk of chronic GVHD.

Our results suggest that patients with late-stage disease benefit from PBSCT rather than BMT. This finding was consistent for all important clinical end points (survival, disease-free survival, relapse). However, statistical tests for interaction did not provide clear evidence of a difference in treatment effect between early- and late-stage disease, and further data are needed to confirm or refute this finding.

In early-stage disease, PBSCT was associated with a lower relapse rate but this did not result in statistically significant better overall or disease-free survival. This could, in part, be a consequence of a large number of patients with chronic phase CML, a disease in which relapse after allogeneic transplant does not immediately lead to death, or alternatively, a reflection of the fact that in early stage disease, nonrelapse mortality is higher compared to relapse-related death.

Although all the trials included in this analysis attempted to address a similar treatment question, they also differed in some details (Table 1). This could have introduced both clinical and statistical heterogeneity into the results. However, except for neutrophil and platelet engraftment, heterogeneity between trials was absent or minimal. Even though the degree of the effects on engraftment was heterogeneous, engraftment was uniformly more rapid after PBSCT than BMT in all trials. This result is biologically plausible.[4,26] Therefore, the observed heterogeneity of treatment effect between trials can be best explained by random fluctuations in the effect size.[27]

One of the main purposes of meta-analyses is to investigate if any bias or play of chance could have affected the results of the analysis.[6] Only if the intervention's effect is greater than that of any of potential biases can the results be considered credible and reliable. The transplant field has traditionally been plagued with selection biases and attrition bias (ie, large imbalance in dropouts between treatment arms).[28] Therefore, paying close attention to the quality of random assignment, which aims to control for selection bias, and accounting for adequate follow-up, to assess for attrition bias is critical.[8] One of the methodological advantages of individual-patient data meta-analysis is to allow assessment of raw data for the quality of

random assignment, concealment of allocation,[29] balance in follow-up, drop-outs, confirmation of internal consistency, and performance of intention-to-treat analyses.[7]

We have performed extensive data checking, including sensitivity analysis within each trial. Our analyses indicated no obvious sources of bias and overall consistent data of high quality. However, we have not controlled for observer bias, which is inherent in the assessment of outcomes such as GVHD[30,31] resulting in poor interobserver agreement.[31] In addition, chance could have affected some of the results because of the large number analyses performed on a relatively small data set.

In the transplantation literature, some trials employ competing risk analysis to address incidence of outcomes such as chronic GHVD.[32] Since the purpose of our study was to compare the effects of PBSCT versus BMT, competing risks analyses were not undertaken as they can be misleading when making treatment comparisons,[32] and methods are not well developed, particularly for use in meta-analysis. Similarly, since the main question being addressed relates to the relative effect of treatments on outcomes, it was inappropriate to evaluate the effect of one outcome (eg, GVHD) on the other (eg, relapse or survival), as well as time-dependent factors.

When choosing between two treatment interventions, a practitioner has to consider both benefits and harms associated with each of the treatment alternatives. Based on this study, PBSCT is associated with faster engraftment, a decrease in relapse and improved disease-free survival when compared with BMT in HLA-identical sibling transplantation for hematologic malignancies. These outcomes were particularly evident in patients with late-stage disease where improved survival was also seen.

Indeed, the largest effect of PBSCT in terms of improvement of disease-free survival and overall survival was seen in patients with late-stage AML and CML. Unfortunately, we could not collect data on cytogenetics to further delineate effect on specific prognostic categories in AML. With regard to treatment of CML, recently, the new standard—imatinib— has emerged as the initial treatment of choice for the management of this disease.[33] Our study was not designed to address the issue of relative merits of imatinib versus allogeneic transplantation. Nevertheless, it does appear that the dramatic shift in the contemporary practice did occur in the sense that fewer patients in the “good” risk category (ie, in chronic phase) are being referred to transplantation. This has resulted in more late-stage CML patients currently undergoing transplantation. Our results show that once patients have progressed to accelerated phase or blast crisis, their disease-free survival and overall survival after allogeneic transplantation are markedly superior after PBSCT compared with BMT.

The incidence of acute GVHD was the same in both PBSCT and BMT although severity (grade 3-4) was greater in recipients of PBSCT. Since more severe GVHD is associated with increased mortality, this very likely accounts for the failure of PBSC to have a beneficial effect on overall survival, despite a lower rate of relapses. This potentially negative effect of peripheral blood stem cells would likely have a greater impact on survival among patients with less advanced leukemias, where rates of relapse are lower.

PBSCT was associated with the increased risk of both limited and extensive chronic GVHD. Extensive chronic GVHD can adversely effect quality of life[34,35] as well as survival,[36,37] but none of the trials included in our meta-analysis collected analyzable data on quality of life. Physicians and patients should weigh the higher risk of disease recurrence with BMT against long-term consequences of chronic GVHD when deciding which stem cell source to use,[38] since chronic GVHD may be an important marker of an active graft-versus-leukemia response and may have been responsible for the reduction in relapse rates and increase in disease-free survival seen with PBSCT. Future research should try to delineate not only harmful effects of

chronic GVHD but its potentially beneficial effects, particularly the impact of milder clinical presentations of chronic GVHD on clinical outcomes in the different clinical subgroups. Ultimately, the choice of treatment should be discussed with the patient, with particular emphasis on these critical trade-offs.

Our analysis reiterates the limitations of small randomized studies.[39] By synthesizing the totality of research evidence we were able to: (1) resolve apparent inconsistencies in clinical outcomes reported by individual trials and (2) identify conclusively important clinical effects that had not been uniformly demonstrated with the previously available information. However, long-term follow-up will still be necessary for fuller understanding of the role of the stem cell source on clinical outcomes since overall follow-up of patients included in our analysis was relatively short.

Authors' Disclosures of Potential Conflicts of Interest

Although all authors have completed the disclosure declaration, the following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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REFERENCES

1. Gratwohl A, Baldomero H, Horisberger B, et al. Current trends in hematopoietic stem cell transplantation in Europe. Blood 2002;100:2374–2386. [PubMed: 12239145]
2. Korbling M, Anderlini P, Hematology TA. Peripheral blood stem cell versus bone marrow allotransplantation: Does the source of hematopoietic stem cells matter. Blood 2001;98:2900–2908. [PubMed: 11698269]
3. Bensinger WI, Clift R, Martin P, et al. Allogeneic peripheral blood stem cell transplantation in patients with advanced hematologic malignancies: A retrospective comparison with marrow transplantation. Blood 1996;88:2794–2800. [PubMed: 8839878]
4. Bensinger WI, Deeg HJ. Blood or marrow. Lancet 2000;355:1199–1200. [PubMed: 10770296]
5. Schmitz N, Barrett J. Optimizing Engraftment-Source and Dose of Stem Cells. Semin Hematology 2002;39:3–14.
6. Early Breast Cancer Trialists Collaborative Group. Worldwide Evidence 1985-1990. Oxford University Press; Oxford, UK: 1990. Introduction and methods section: Treatment of Early Breast Cancer.
7. Stewart L, Clark M. For the Cochrane Collaboration Working Group on meta-analyses using individual patient data: Practical methodology of meta-analyses (overviewes) using updated individual patient data. Stat Med 1995;14:1057–1079. [PubMed: 7569500]
8. Clarke, M.; Oxman, AD. Cochrane Reviewer's Handbook 4.1 [update July 2000], in Review Manager (Revman) [Computer Program]. version 4.1. The Cochrane Collaboration; Oxford: 1999.
9. Clark, L.; Clark, O.; Wheatley, K., et al. The Cochrane Library, Issue 4, 2003. John Wiley & Sons, Ltd; Chichester, UK: 2003. Allogeneic peripheral blood stem cells transplantation versus bone marrow transplantation for the therapy of hematological malignancies (Protocol for a Cochrane Review).
10. Clarke, M.; Stewart, L. Obtaining individual patient data from randomised controlled trials. In: Egger, M.; Smith, GD.; Altman, DG., editors. Systematic Reviews in Health Care: Meta-Analysis in Context. BMJ; London, UK: 2001.
11. The Myeloma Trialists' Collaborative Group. Intereferon as therapy for multiple myeloma: An individual patients data overview of 24 randomized trials and 4012 patients. 2001;113:1020–1034.
12. Early Breast Cancer Trialists Collaborative Group. Polychemotherapy for early breast cancer: An overview of the randomized trials. Lancet 1998;352:930–942. [PubMed: 9752815]
13. Morton J, Hutchins C, Durant S. Granulocyte-colony-stimulating (G-CSF)-primed allogeneic bone marrow: significantly less graft-versus-host disease and comparable engraftment to G-CSF-mobilizau peripheral blood stem cells. Blood 2001;98:3186–3191. [PubMed: 11719353]
14. Vigorito AC, Azevedo WM, Marques JF, et al. A randomised, prospective comparison of allogeneic bone marrow and peripheral blood progenitor cell transplantation in the treatment of haematological malignancies. Bone Marrow Transplant 1998;22:1145–1151. [PubMed: 9894716]
15. Vigorito AC, Comenalli Marques JF, Penteado Aranha FJ, et al. A randomized, prospective comparison of allogeneic bone marrow and peripheral blood progenitor cell transplantation in the

treatment of hematologic malignancies: An update. Haematologica 2001;86:665–666. [PubMed: 11418381]

16. Couban S, Simpson D, Barnett MJ, et al. A randomized multicenter comparison of bone marrow and peripheral blood in recipients of matched sibling allogeneic transplants for myeloid malignancies. Blood 2002;100:1525–1531. [PubMed: 12176866]
17. Schmitz N, Beksac M, Hasenclever D, et al. Transplantation of mobilized peripheral blood cells to HLA-identical siblings with standards-risk leukemia. Blood 2002;100:761–767. [PubMed: 12130483]
18. Mahmoud H, Fahmy O, Kamel A, et al. Peripheral blood vs bone marrow as a source for allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant 1999;24:355–358. [PubMed: 10467322]
19. Blaise D, Kuentz M, Fortanier C, et al. Randomized trial of bone marrow versus lenograstim-primed blood cell allogeneic transplantation in patients with early-stage leukemia: A report from the Societe Francaise de Greffe de Moelle. J Clin Oncol 2000;18:537–546. [PubMed: 10653869]
20. Cornelissen JJ, van der Holt B, Petersen EJ, et al. A randomized multicenter comparison of CD34+-selected progentor cells from bone marrow in recipients of HLA-identical allogeneic transplants for hematological malignancies. Exp Hematol 2003;31:1–10. [PubMed: 12543102]
21. Heldal D, Tjonnfjord G, Brinch L, et al. A randomised study of allogeneic transplantation with stem cells from blood or bone marrow. Bone Marrow Transplant 2000;25:1129–1136. [PubMed: 10849524]
22. Powles R, Mehta J, Kulkarni S, et al. Allogeneic blood and bone-marrow stem-cell transplantation in haematological malignant diseases: A randomised trial. Lancet 2000;355:1231–1237. [PubMed: 10770306]
23. Bensinger WI, Martin PJ, Storer B, et al. Transplantation of bone marrow as compared with peripheral-blood cells from HLA-identical relatives in patients with hematologic cancers. N Engl J Med 2001;344:175–181. [PubMed: 11172139]
24. Moher D, Cook D, Eastwood S, et al. Improving the quality of reports of meta-analyses of randomised controlled trials: The QUOROM statement. Lancet 1999;354:1896–1900. [PubMed: 10584742]
25. Cutler, C.; Antin, JH. Stem cell sources: Peripheral blood stem cells and bone marrow for allogeneic transplantation. In: Soiffer, RJ., editor. Stem Cell Transplantation for Hematologic Disorders. Humana Press; 2004. p. 337-356.
26. Bensinger WI, Weaver CH, Appelbaum FR, et al. Transplantation of allogeneic peripheral blood stem cells mobilized by recombinant human granulocyte colony-stimulating factor. Blood 1995;85:1655–1658. [PubMed: 7534140]
27. Petiti, DB. Meta-Analysis, Decision Analysis and Cost-Effectiveness Analysis: Methods for Quantitative Synthesis in Medicine. ed 2. Oxford Press; New York, NY: 2000.
28. Wheatley K. SAB-a promising new treatment to improve remission rates in the elderly. Br J Haematol 2002;118:432–433. [PubMed: 12139727]
29. Schulz KF, Chalmers I, Hayes R, et al. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA 1995;273:408–412.
30. Massi D, Franchi A, Pimpinelli N, et al. A reappraisal of the histopathologic criteria for the diagnosis of cutaneous allogeneic acute graft-vs-host disease. Am J Clin Pathol 1999;112:791–800. [PubMed: 10587702]
31. Vogelsang GB. How I treat chronic graft-versus-host disease. Blood 2001;97:1196–1201. [PubMed: 11222360]
32. Gooley T, Leisenring W, Crowley J, et al. Estimation of failure probabilities in the presence of competing risks: New representations of old estimators. Stat Med 1999;18:695–706. [PubMed: 10204198]
33. Peggs K, Mackinnon S. Imatinib mesylatethe new gold standard for treatment of chronic myeloid leukemia. N Engl J Med 2003;348:1048–1050. [PubMed: 12637616]
34. Lee S, Cook EF, Soiffer R, et al. Development and validation of a scale to measure symptoms of chronic graft-versus-host disease. Biol Blood Marrow Transplant 2002;8:444–452. [PubMed: 12234170]

35. Sullivan K. Longterm followup and quality of life after hematopoeitic stem cell transplantation. J Rheumatol Suppl 1997;48:46–52. [PubMed: 9150118]

36. Goerner M, Gooley T, Flowers ME, et al. Morbidity and mortality of chronic GVHD after hematopoietic stem cell transplantation from HLA-identical siblings for patients with aplastic or refractory anemias. Biol Blood Marrow Transplant 2002;8:47–56. [PubMed: 11858190]

37. Miflin G, Russell NH, Franklin I, et al. An analysis of the effect of chronic GvHD on relapse and survival following allogeneic PBSC transplantation. Cytotherapy 2000;2:423–428. [PubMed: 12044222]

38. Mohty M, Kuentz M, Michallet M, et al. Chronic graft-versus-host disease after allogeneic blood stem cell transplantation: Long-term results of a randomized study. Blood 2002;100:3128–3134. [PubMed: 12384409]

39. Collins R, McMahon S. Reliable assessment of the effects of treatment on mortality and major morbidity, I: Clinical trials. Lancet 2001;357:373–380. [PubMed: 11211013]

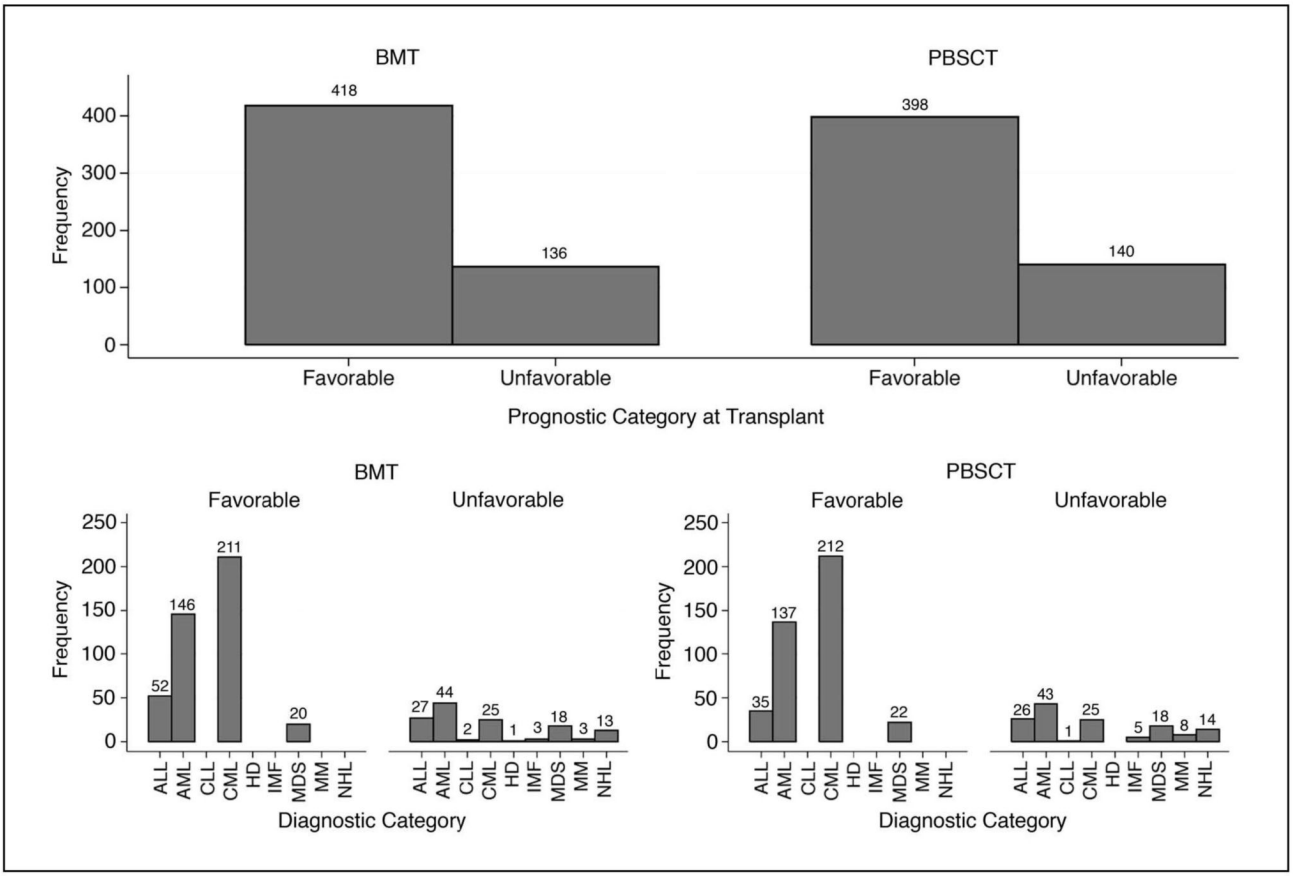

Fig 1.

The patient distribution according to the type of diagnosis and its prognostic features (favorable = early-stage disease; unfavorable = late-stage disease; see text for details). BMT, bone marrow transplantation; PBSCT, peripheral blood stem-cell transplantation; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; MDS = myelodysplastic syndrome; HD, Hodgkin's disease; NHL, non-hodgkin lymphoma; CLL, chronic lymphocytic leukemia; MM, multiple myeloma; IMF, idiopathic myelofibrosis.

Fig 2.

Summary forest plot showing the effects of allogeneic peripheral blood stem cell transplantation (PBSCT) versus bone marrow transplantation (BMT). If the square is to the left of the solid line then odds ratio (OR) is better in the group receiving PBSC, but if the CI crosses this line, then this result is not statistically significant ($P < .05$). GVHD, graft-versus-host disease; c, chronic; a, acute; O – E, observed – expected; Var., variance; Redn., reduction; SD, standard deviation.

Fig 3.
(A) Time-to-event plots showing the absolute risk for development of grade 2-4 acute graft-versus-host-disease (GVHD) in patients with hematologic malignancies. (B) Time-to-event plots showing the absolute risk for development of grade 3-4 acute GVHD in patients with hematologic malignancies. PBSCT, peripheral blood stem-cell transplantation; BMT, bone marrow transplantation; abs diff, absolute difference.

Fig 4.
(A) Time-to-event plots showing the absolute risk for development of extensive stage of chronic graft-versus-host disease (GVHD) in the patients with hematologic malignancies. (B) Time-to-event plots showing the absolute risk for development of any stage of chronic GVHD in patients with hematologic malignancies. PBSCT, peripheral blood stem-cell transplantation; BMT, bone marrow transplantation; Abs diff, absolute difference.

Fig 5.
Time-to-event plots showing the risk of relapse in patients with hematologic malignancies treated with allogeneic peripheral blood stem-cell transplantation (PBSCT) versus bone marrow transplantation (BMT). Abs diff, absolute difference.

Fig 6.
Time-to-event plots showing the risk of relapse in patients with hematologic malignancies treated with allogeneic peripheral blood stem-cell transplantation (PBSCT) versus bone marrow transplantation (BMT). (A) In early-stage disease and (B) in late-stage disease. Abs diff, absolute difference.

Fig 7.

(A) Relapse-related mortality. Time-to-event plots showing the absolute risk reductions in relapse mortality in patients with hematologic malignancies treated with allogeneic peripheral blood stem-cell transplantation (PBSCT) versus bone marrow transplantation (BMT). (B) Time-to-event plots showing the absolute risk reductions in death without relapse (nonrelapse mortality) in patients with hematologic malignancies treated with allogeneic PBSCT versus BMT. Abs diff, absolute difference.

Fig 8.

Survival curves showing the absolute risk reductions in disease-free survival in patients with hematologic malignancies treated with allogeneic peripheral blood stem-cell transplantation (PBSCT) versus bone marrow transplantation (BMT). Differences at 3- and 5-year outcome, together with the SEs, and two-sided *P* values are given in the box. Abs diff, absolute difference.

Fig 9.
Survival curves showing the absolute risk reductions in disease-free survival in patients with hematologic malignancies treated with allogeneic peripheral blood stem-cell transplantation (PBSCT) versus bone marrow transplantation (BMT). (A) In early-stage disease, (B) in late-stage disease. Abs diff, absolute difference.

Fig 10.
Forest plot illustrating the effect of peripheral blood stem-cell transplantation (PBSCT) versus bone marrow transplantation (BMT) on overall survival. Note: inclusion of Egyptian trial (N = 29) from which data on individual patients were not available (data from this trial were extracted from the paper). Inclusion of this trial did not change the results significantly (see the main text for details). NS, not significant; OR, odds ratio; EBMT, European Group for Blood and Marrow Transplantation; O – E, observed – expected; Var., variance; Redn., reduction; SD, standard deviation.

Fig 11.
Survival curves showing the absolute risk reductions in death in patients with hematologic malignancies treated with allogeneic peripheral blood stem-cell transplantation (PBSCT) versus bone marrow transplantation (BMT). Abs diff, absolute difference.

Fig 12.
Survival curves showing the absolute risk reductions in death in patients with hematologic malignancies treated with allogeneic peripheral blood stem-cell transplantation (PBSCT) versus bone marrow transplantation (BMT). (A) In early-stage disease, (B) in late-stage disease. Abs diff, absolute difference.

Table 1.

General Characteristics of the Randomized Clinical Trials That Compared PBSCT Versus BMT for the Treatment of Hematologic Malignancies

Trial	Comparison	Eligibility Criteria	Setting	G-CSF Dose Employed for PBSC Mobilization	Routine G-CSF Posttransplantation	GVHD Prophylaxis *	Patients Characteristics				Conditioning Regimen	Notable Outcomes
							Median Age (years)	Age Range (years)	Males			
									No.	%		
Australia † Morton et al, 2001 (N = 57)	G-PBSCT versus G-BMT	HLA-identical sibling donors Hematologic malignancies Patients 10-60 years old	Single-center	10 μg/kg/5d (Filgrastim)	No	CSA/MTX (D+1,3,6)	45	16-60	27	48.2	TBI: 10 (18%) No TBI: 47 (82%)	Less chronic GVHD in BMT arm (p < .02) †
Brazil Vigorito et al, 1998 (N = 56)	PBSCT versus BMT	HLA-identical sibling donors Hematological malignancies Patients 16-65 years old	Single-center	10 μg/kg/5d (Filgrastim)	No	CSA/MTX (D+1,3,6,11) or CSA/ PRED (3 patients in BMT arm)	31	7-60	38	67.8	TBI: 3 (5%) No TBI: 53 (95%)	Less extensive chronic GVHD in BMT arm (p = .02)
Canada Couban et al, 2002 (N = 228)	PBSCT versus BMT	CML (in chronic or accelerate phase), AML (in remission), and MDS HLA-matched sibling donor	Multi-center	5 μg/kg/4d (Filgrastim)	No	CSA/MTX (D+1,3,6,11)	45	19-65	133	58.3	No TBI: 228 (100%)	Trend to lower nonrelapse mortality in the PBSCT arm Survival advantage for PBSCT (HR = 0.62, 95% Cl 0.39-0.97, p = .04
EBMT/ Amgen Schmitz et al, 2002 (N = 350)	PBSCT versus BMT	Patients 16-55 years old De novo AML and ALL (in 1st or 2nd remission or in 1st incipient relapse), CML (in chronic or accelerate phase), MDS (except RAEBT) HLA-identical sibling donors	Multi-center	10 μg/kg/4d (Filgrastim)	Yes 5 μg/kg/d	CSA/MTX (D+1,3,6)	38	17-58	196	56.0	TBI: 214 (65%) No TBI: 117 (35%)	Less acute GVHD in BMT arm (*P* = .013) Less chronic GVHD in

Trial	Comparison	Eligibility Criteria	Setting	G-CSF Dose Employed for PBSC Mobilization	Routine G-CSF Posttransplantation	GVHD Prophylaxis *	Patients Characteristics					
							Median Age (years)	Age Range (years)	Males		Conditioning Regimen	Notable Outcomes
									No.	%		
												BMT arm (P = .0066)
Egypt ‡ Mahmoud et al, 1999 (N = 30)	PBSCT versus BMT	Patients 16-42 years old HLA-identical sibling donors Any hematologic malignances	Single-center	10 μg/kg/4d (Filgrastim)	Yes 10 μg/kg/d	CSA/MTX (D+1,3,6,11)	22	16-42	23	76.6	TBI: 29 (97%) No TBI: 1 (3%)	Less acute GVHD in PBSCT arm (P = .013)
France Blaise et al, 2000 (N 101)	PBSCT versus BMT	Patients < 55 years old ALL, AML and CML (1st chronic phase), HLA-matched sibling donor	Multi-center	10 μg/kg/4d (Lenograstim)	No	CSA/MTX (D+1,3,6)	36	16-53	53	52.5	TBI: 86 (85%) No TBI: 15 (15%)	Less chronic GVHD in BMT arm
Netherlands Cornelissen et al, 2003 (N 120)	T-cell depleted (TCD) PBSCT versus TCD BMT	Patients 16-60 years old AML, ALL, MDS, MM, NHL HLA-identical sibling donors	Multi-center	10 μg/kg/5d (Filgrastim)	No	CSA/MTX (D+1,3,6,11)	22	16-42	23	76.6	TBI: 29 (97%) No TBI: 1 (3%)	Less acute GVHD in PBSCT arm (P = .013)
Norway Heldal et al, 2000 (N = 61)	PBSCT versus BMT	Patients 15-60 years old AML, ALL, CML, PMF and MDS HLA-identical sibling donors or one mismatched family donor	Single-center	10 μg/kg/5d (Filgrastim)	No	CSA/MTX (D+1,3,6)	36	16-53	53	52.5	TBI: 86 (85%) No TBI: 15 (15%)	Less chronic GVHD in BMT arm Survival advantage for BMT [HR = 1.7, 95% Cl, 1.0 to 3.0: P = .04] †
Saudi Arabia (unpublished) (N = 83)	PBSCT versus BMT	Hematologic malignances HLA-identical sibling donors			No	CSA	41	18-60	76	63.3	TBI: 107 (89%) No TBI: 3 (3%)	No difference in outcomes noted, except faster engraftment
UK Powles et al, 2000 (N = 39)	PBSCT versus BMT	Patients 15-55 years old Any hematologic malignances HLA-identical sibling donors	Multi-center	10 μg/kg/5d (Lenograstim)	No	CSA/MTX (D+1,3,6,11)	42	15-55	38	62.3	No TBI: 61 (100%)	

Trial	Comparison	Eligibility Criteria	Setting	G-CSF Dose Employed for PBSC Mobilization	Routine G-CSF Posttransplantation	GVHD Prophylaxis *	Patients Characteristics				Conditioning Regimen	Notable Outcomes
							Median Age (years)	Age Range (years)	Males			
									No.	%		
Bensinger et al, 2003 US1 (N = 176)	PBSCT versus BMT	Patients 12-55 years old Hematologic malignances HLA-identical sibling donors	Multi-center	16 μg/kg/5d (Filgrastim)	No		23	15-48	45	54.2	TBI: 14 (18%) No TBI: 62 (82%)	in PBSCT arm No difference in survival, disease free survival, and relapse Reduction in relapse for PBSCT [HR = 0.37, 95% Cl, 0.17 to 0.68 *P* = .01] Disease-free survival advantage for PBSCT [HR = 0.60, 95% Cl, 0.38 to 0.95, *P* = .03] Reduction in relapse for PBSCT [HR = 0.49, 95% Cl, 0.24 to 1.00, *P* = .04] No difference in survival, and disease free survival No relapse noted in either arm
US2 (unpublished) (N = 18)	PBSCT versus BMT	CML HLA-identical sibling donors				CSA/MTX (D+1,3,6,11)	37	22-52	29	74.3	TBI: 24 (62%) No TBI: 15 (38%)	
						CSA/MTX (D+1,3,6,11)	42	12-56	122	69.3	TBI: 102 (59%) No TBI: 71 (41%)	
							46	19-61	12	66.7	No TBI: 18 (100%)	

Abbreviations:

GVHD

graft versus host disease

G-CSF

granulocyte colony-stimulating-factor

BMT
bone marrow transplantation

PBSCT
peripheral blood stem-cell transplantation

ALL
acute lymphoblastic leukemia

AML
acute myeloid leukemia

CML
chronic myeloid leukemia

MDS
myelodysplastic syndrome

PMF
primary myelofibrosis

NHL
non-Hodgkin's lymphoma

RAEBT
refractory anemia with excess blast in transformation

TBI
total-body irradiation

Bu
busulfan

Cy
cyclophosphamide

CSA
cyclosporine A

MTX
methotrexate

Pred
prednisone

EBMT
European Group for Blood and Marrow Transplantation

* The dose of methotrexate used for the prophylaxis of GHVD was 15 mg/kg on D1 and 10 mg/kg on the rest of the days (D3, D6, and D11). Three patients in the Brazilian trial received prednisone. Initially, intravenous dose of cyclosporine was used in all trials in a dose ranging between 2-5 mg/kg with later switch to oral dose and administration according to blood levels.

† Design of these trials was considered to significantly differ from the rest of the trials; therefore, they were not included in the pooled analysis (see text for details). They are listed here to provide readers with information on all existing randomized evidence in the field.

‡ Published data only.