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Individual patient data meta-analysis of allogeneic peripheral blood stem cell transplant vs bone marrow transplant in the management of hematological malignancies: indirect assessment of the effect of day 11 methotrexate administration

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Abstract

The effects of immunosuppressive regimens on the outcomes of patients with hematological malignancies undergoing allogeneic stem cell transplantation remain uncertain. We conducted an individual patient data meta-analysis using data from nine randomized trials comparing allogeneic peripheral blood stem cell (PBSCT) transplants to bone marrow (BMT) transplants, focusing on the administration of three vs four doses of methotrexate (MTX) as part of a regimen for graft-versus-host-disease (GVHD) prophylaxis which included cyclosporine. Six trials containing 573 patients prescribed four doses of MTX while three trials containing 534 patients prescribed three doses of MTX. Four doses of MTX conferred a statistically significant survival advantage, resulting in death odds ratio (OR) 0.67 (CI 0.52–0.88) (P=0.0036) for recipients of PBSC compared to BM; with three doses, there was no statistically significant difference. In the four-dose studies relapse rates were 36.6% among recipients of BM compared to 19.2% among recipients of PBSC (P=0.0015). The rates of relapse in the three dose studies were 26% for both PBSC and BM. We hypothesize that the fourth dose of MTX provides extra immunosuppression among BM recipients resulting in a reduced anti-leukemic effect. This hypothesis can only be proved or disproved by a prospective, randomized trial.

Keywords

allogeneic; peripheral blood stem cells; bone marrow; methotrexate

Introduction

Peripheral blood stem cells (PBSC) have replaced bone marrow (BM) as the preferred source of hematopoetic stem cells used for autologous transplantation. Recent surveys indicate that PBSC are used in 50–60% of allogeneic stem-cell transplants.[1] The relative effects of allogeneic PBSC transplant vs BM transplant on the outcomes of patients with hematological malignancies are uncertain. In order to address this question, several randomized controlled trials have been conducted. Despite several well designed and executed clinical trials, when taken individually, most of these trials were too small to draw definitive conclusions and, not surprisingly, substantial controversy still remains regarding the impact on graft-versus-host-disease (GVHD), mortality, disease control and other important clinical outcomes.[2–4]

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This is a common situation in health care research and demonstrates the need for a systematic review of 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 is centrally collected, processed and analyzed.[5,6] The Stem Cell Trialists Collaborative Group have published results of the first analysis comparing global outcomes of randomized studies comparing PBSC to BM.[7] The analysis found that PBSC are associated with a decrease in the rates of relapse, which may improve disease-free and overall survival in patients with late-stage disease. The use of PBSC was associated, however, with an increased risk of chronic GVHD.

It is not clear which drugs and schedules for prevention of GVHD are optimum and whether the effects of these drugs differ depending on the stem cell source. Here, we report the second analysis of IPD-MA examining the effect of day 11 methotrexate on the outcomes between HLA-matched, related allogeneic PBSCT and BMT as therapy for hematological malignancies.

Methods

The lead authors from published randomized trials comparing allogeneic PBSC with BM[8–18] were contacted and agreed to collaborate and contribute updated individual patient data to this effort. Procedures for the meta-analysis based on the individual patient data have been published in our first report and followed recommended procedures.[5–7,19]

Statistical methods

Extensive data checking was performed using methods described previously.[5,6,19,20] First, data were checked for obvious inconsistencies and amended as necessary through intensive correspondence with the responsible principal investigators. Raw data were also compared with aggregate data in available publications. Particular attention was given to the quality of the randomization procedure used in each trial and the elements of the trials' quality assessment. This was carried out by checking for any imbalance in accrual between two randomized arms, follow-up and length of follow-ups and the numbers in subgroups.

All comparisons were based on the intention-to-treat principle. Individual patient data allow 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.[5,20,21] The individual log-rank statistics were combined to give an overall estimate of the effect of PBSCT vs BMT on the outcomes of interest. When information from different trials is combined in this way, the patients in a given trial are compared directly only with other patients[5] in the same trial, and not with the patients in another trial.[6,20,21] The individual patient data are never pooled in such an analysis. The combination of data from different trials yields an overall estimate of the effect of treatment in all trials, which is then used to calculate reductions in odds of death or other outcomes of interest. All *P*-values are two-tailed. The results are expressed in such a way that a proportional reduction of a quarter in the annual odds of death might equivalently be described as an odds ratio of 0.75, a hazard ratio of 0.75, an odds reduction of 25%, or a 25% reduction in the death rate.[5,21] To test for the difference between overall effect size and the measure of effect from each study a statistical test for heterogeneity was performed across all trials as well as between the subgroups.[5] All subgroup analyses were defined *a priori.*

Differences in the effects between subgroups of patients who were given four doses of MTX vs those who were given three doses, were formally investigated using tests for heterogeneity (interaction) to assess whether the effect size might be different among the studies/subgroups,

that is, if observed variability in results is greater than that expected to occur by chance. The main endpoints analyzed were: overall survival, relapse or 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 transplant and day + 100 after the transplant, respectively. Disease-free survival was defined as time to death or relapse, whichever occurred first.

A uniform consensus among all trialists was achieved to separate disease in those with 'good' prognostic features (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 'poor' prognostic features (CML in second chronic phase, accelerated phase or blast crisis; AML or ALL, refractory or in greater than first remission; refractory anemia with excess blasts or in transformation subtypes of MDS, multiple myeloma, Hodgkin's disease, non-Hodgkin's lymphoma, and idiopathic myelofibrosis).

Results

Trials and patients

While some differences existed among the trials, it was felt that all trials tested similar interventions for similar conditions under similar circumstances to allow combining their results in this meta-analysis.[5] Individual patient data from one trial (n=29) were not provided,[22] and not included in this analysis. Thus, data on 1107 patients from nine trials were included in the final analysis. There were 6 randomized trials comprised of 573 patients where 4 doses of MTX (days 1, 3, 6 and 11) were prescribed in combination with cyclosporine for prophylaxis of GVHD. In three trials, comprised of 534 patients, MTX was given on days 1, 3 and 6 in combination with cyclosporine. Overall, treatment groups appeared well balanced according to the most important prognostic features (i.e. age, sex, disease type, etc). Characteristics of each trial and the patients included are listed in Table 1.

Engraftment

Both neutrophils and platelets engrafted sooner in the PBSCT arm, regardless of whether three or four doses of MTX were prescribed.

The test for interaction between two subgroups was highly significant: $\chi^2 = 11.4$; $P<0.0008$ for platelet engraftment. No such difference was noted for neutrophil engraftment (test for interaction: $\chi^2 = 0.6$; $P = 0.4$).

Acute GVHD

Overall 40% of patients developed grade II–IV acute GVHD and 30% developed grades III–IV acute GVHD. There were no differences in the risks of acute GVHD grades II–IV between recipients of PBSC or BM, irrespective of whether patients were assigned to received day 11 MTX (OR = 1.09, 95% CI 0.82–1.43, $P = 0.55$) or not (OR = 1.22, 95% CI 0.91–1.63, $P = 0.19$). Risk of grades III–IV acute GVHD was similar among recipients prescribed day 11 MTX but among patients not assigned day 11 MTX there was a trend to more GVHD with recipients of PBSC (OR 1.50, 95% CI 0.99–2.29, $P = 0.058$). The test for interaction between subgroups of patients receiving day 11 MTX and those who did not was not significant (for grade II–0-IV, $\chi^2 = 0.3$; $P<0.6$; for grade III–IV, $\chi^2 = 0.3$; $P = 0.6$).

Chronic GVHD

There was a very significant increase in the odds of developing chronic GVHD, both extensive and any stage, in patients treated with PBSC, irrespective of whether patients received day 11

MTX, any stage (OR = 1.43, 95% CI = 1.51–3.23, $P<0.016$), or did not, any stage (OR = 1.96, 95% CI = 1.45–2.65, $P<0.00001$) (Figure 1a and b show chronic extensive GVHD). The test for interaction between subgroups of patients receiving day 11 MTX and those who did not was not significant (for chronic extensive GVHD, $\chi^2 = 1.7$, $P = 0.2$).

Non-relapse mortality

Among patients assigned to day 11 MTX, non-relapse mortality was 31% in PBSC recipients vs 36% in recipients of BM, $P = 0.06$. This trend was reversed among patients who did not receive day 11 MTX, at 35% among recipients of PBSC vs 26% among recipients of BM, $P = 0.057$. The test for interaction between subgroups of patients receiving day 11 MTX and those who did not was significant (for non-relapse mortality, $\chi^2 = 7.0$, $P = 0.008$).

Relapse and relapse-related mortality

Among patients who were assigned to day 11 MTX the risk of relapse at 6 years was 19% in patients receiving PBSC vs 37% in BM recipients, $P = 0.0015$ (OR 0.54, 95% CI 0.37–0.79) (Figure 2a). In patients who were not assigned to receive day 11 MTX the incidence of relapse was 27% for both recipients of PBSC or BM (Figure 2b). Mortality due to relapse occurred in 24% of patients who received day 11 MTX and BM, compared to 14% in recipients of PBSC, $P = 0.018$ (OR 0.58, 95% CI 0.37–0.91). The difference in relapse-related mortality among patients who did not receive day 11 MTX was 13% for PBSC and 14% for BM, $P = 0.39$. The test for interaction between subgroups of patients receiving day 11 MTX and those who did not was significant (for relapse, $\chi^2 = 3.9$, $P = 0.05$).

Disease-free survival

Assignment to day 11 MTX was associated with a significant improvement in disease-free survival (DFS) in recipients of PBSC compared to BM (OR 0.62, 95% CI 0.48–0.80, $P = 0.00023$). The improvement in DFS with day 11 MTX and PBSC was seen both in patients with early stage disease (OR 0.63, 95% CI 0.44–0.89, $P = 0.009$) and late stage disease (OR 0.59, 95% CI 0.40–0.86, $P = 0.0065$). Among the studies that did not use day 11 MTX, there was no difference in DFS between recipients of PBSC vs BM (OR 1.1, 95% CI 0.83–1.45, $P = 0.51$). The test for interaction between subgroups of patients receiving day 11 MTX and those who did not was significant (for disease-free survival, $\chi^2 = 8.7$, $P = 0.003$).

Survival

Overall survival (OS) was significantly better among recipients of PBSC compared to BM in studies where day 11 MTX was prescribed (OR 0.67, 95% CI 0.52–0.88, $P = 0.004$). There were no differences in OS between PBSC and BM in studies that did not prescribe day 11 MTX (OR 1.19, 95% CI 0.89–1.60, $P = 0.2$) (Figure 3a and b). Figure 4 is a tree diagram that summarizes the individual contributions of the nine studies on survival, segregated by whether or not the day 11 methotrexate was prescribed. Note that individually, none of the studies had sufficient power to observe statistically significant differences.

The test for interaction between subgroups of patients receiving day 11 MTX and those who did not was significant (for overall survival, $\chi^2 = 8.0$, $P = 0.005$).

Discussion

To address questions regarding the relative advantages and disadvantages of hematopoietic stem cells sources, the stem cell trialists' collaborative group conducted the first IPD-MA of prospective randomized trials examining transplantation of HLA-matched, related allogeneic PBSC and BM in patients with hematologic malignancies.[7] In the first analysis it was found

that allogeneic transplants with PBSC were associated with reduced relapse rates and improved disease-free and overall survival primarily in patients with late stage disease. PBSC were also associated with significantly more chronic GVHD.

The present analysis was undertaken primarily to define the relative roles of GVHD prophylaxis when PBSC or marrow are used. This current analysis found that the relative effect of PBSC and BM on disease-free and overall survival was significantly different between the subgroups of trials, defined by whether the administration of day 11 MTX was part of the protocol. This difference was due primarily to a significantly lower rate of relapse and relapse-related deaths among recipients of PBSC in the four dose MTX trials. There were no statistically different rates of transplant-related deaths between recipients of PBSC or BM, regardless of whether three or four doses of MTX were prescribed, although trends for non-relapse mortality were reversed; favoring PBSC when day 11 MTX was given and BM when day 11 MTX was not. In trials prescribing only three doses of MTX there were no differences in relapse or survival between PBSC and BM. The differences in relapse rates between the four dose MTX recipients of BM or PBSC could be due to a lower relapse rate among PBSC recipients, a higher relapse rate in recipients of BM or a combination of both. Unfortunately, the meta-analysis does not allow direct comparisons of relapse rates of either BM recipients or PBSC recipients between the three dose MTX and four dose MTX studies. This is in part due to differences in the mix of risk factors between the different studies and because it is important to preserve randomization of patients within each study.

The combination of MTX and cyclosporine has been widely adopted as the preferred regimen for prevention of GVHD due to its superior efficacy compared to single agent MTX or CSP.[23] The close interactions of GVHD prophylaxis, GVHD and relapse after allogeneic BM transplant are well known. Some, but not all studies have identified an association between more intensive immunosuppressive regimens and higher rates of relapse.[24] In a long-term follow-up of a randomized trial of MTX and cyclosporine versus cyclosporine alone in patients undergoing allogeneic BM transplant, Storb *et al*.[23] found increased leukemia relapses in patients with acute non-lymphocytic leukemia, but not in patients with CML. In an analysis of 199 HLA identical sibling donor transplants, Nordlander *et al*.[25] found that combination GVHD prophylaxis with MTX and cyclosporine was associated with a greater risk of relapse (HR 2.56, OR 1.22–5.37, $P = 0.01$) compared to single agent MTX or cyclosporine. A retrospective study from the International Bone Marrow Transplant Registry found no differences in relapse rates among patients with leukemia receiving cyclosporine alone or combined with MTX. These studies included patients with differing MTX schedules and also included patients who had received prednisone as part of GVHD prophylaxis, and this mixture of patients could have easily obscured the effects of MTX dosing.[26] In our study, the MTX schedules, whether they were prescribed for 3 or 4 days were uniform across the trials as shown in Table 1.

The reasons why four doses of MTX might have such a differential effect on outcomes that are dependent on stem cell source are not entirely clear. It is well established that MTX containing regimens slow the rates of neutrophil and platelet engraftment. In the present analysis, neutrophil and platelet engraftment occurred more rapidly and with a higher percentage of patients achieving engraftment in recipients of PBSC regardless of whether or not the fourth dose of MTX was given.

The administration of the fourth dose of MTX may provide critical immunosuppression by causing apoptosis of rapidly dividing lymphocytes at the time of early engraftment. This could impair the antileukemia effects of donor lymphocytes. More recent studies suggest that low dose MTX may prevent activation of T cells rather than apoptosis.[27] We speculate that these effects could be more pronounced in recipients of BM compared to PBSC due to the 1 log

greater numbers of T cells. In addition, the differential sensitivity of specific diseases to GVL effects are well known.[23] As the IPD-MA contained patients with a variety of different diseases, the GVL effect may be more or less apparent depending on the mix of diagnoses within a given study.

Our analysis should be interpreted within the context of the extreme logistical difficulties associated with performing large randomized trials in allogeneic transplantation. As hematological diseases are rare, and transplant numbers are relatively low even in large centers, most trials had to enroll patients with a variety of hematological malignancies containing a mix of standard risk and high-risk patients. However, by putting together the results of all existing trials we were able to increase the power of the analysis.

To date, no randomized studies have examined whether the administration of three or four doses of MTX in combination with cyclosporine affects any outcomes in recipients of allogeneic PBSC or BM. The present report suggests that further prospective studies to test these observations are warranted.

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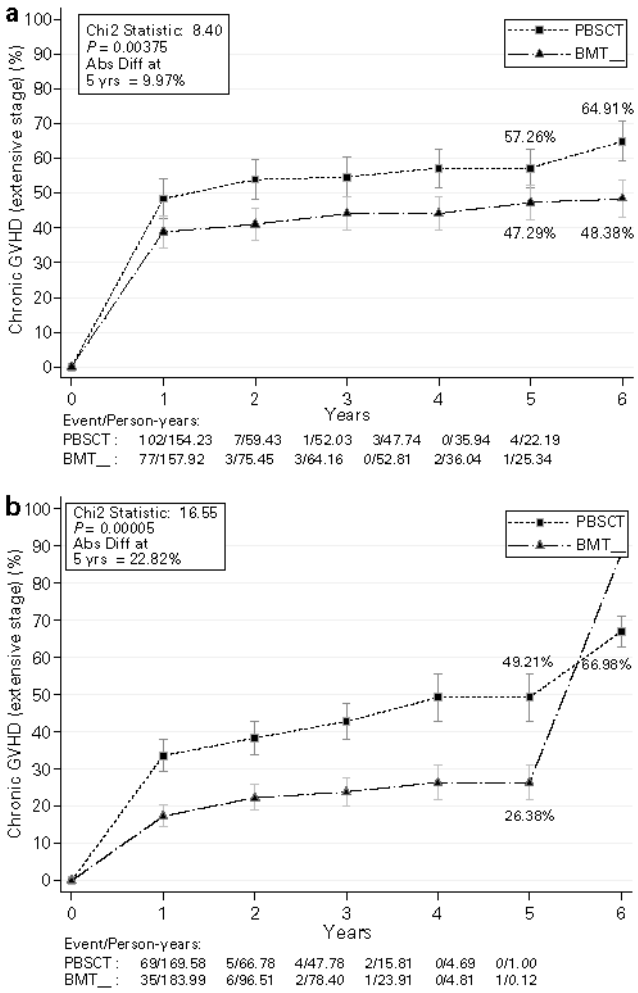

Figure 1.

Time-to-event plots showing the absolute risk for development of extensive chronic graft-versus-host disease in the patients with hematologic malignancies who received four doses (**a**) or three doses (**b**) of MTX. There is more chronic GVHD of any stage in patients treated with allogeneic PBSC regardless of the MTX doses.

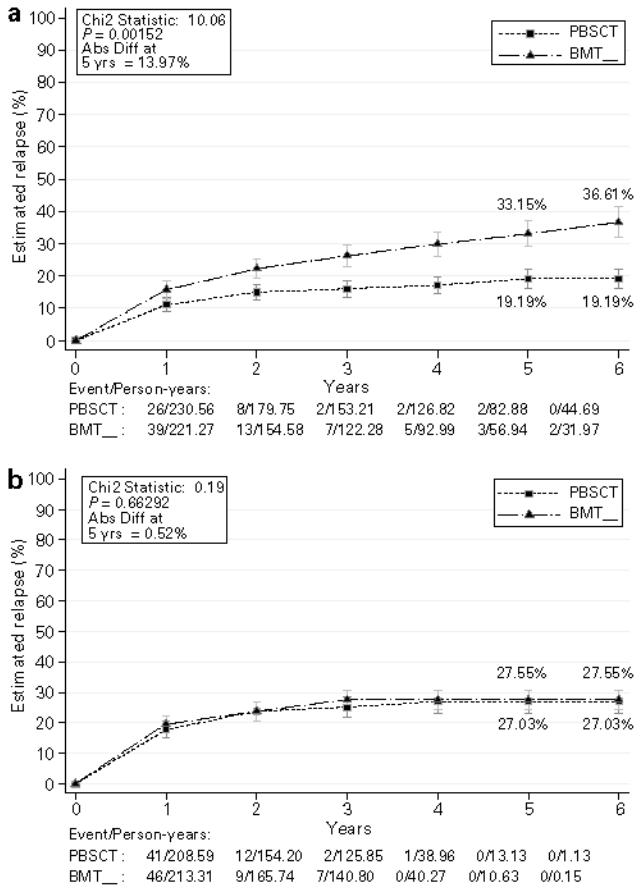

Figure 2.

Time-to-event plots showing the absolute risk for development of relapse in the patients with hematologic malignancies who received 4 doses of MTX, all patients (**a**), and all patients who received only 3 doses of MTX (**b**).

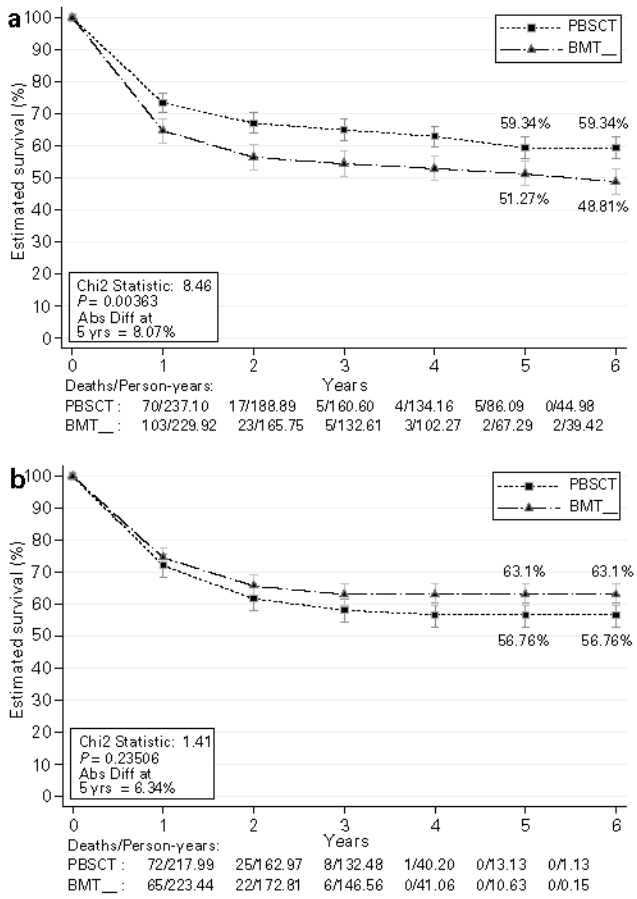

Figure 3.

Survival curves showing the absolute risk reductions in death during the first 6 years of transplant with allogeneic PBSC vs BM depending on whether four doses of MTX (a) or three doses of MTX (b) were given. There was statistically better survival among recipients of PBSC compared to BM in the four dose MTX studies. No statistically significant differences were seen among recipients of PBSC or BM in the three dose trials. Differences in 5-year outcome, together with the standard errors, and two-sided *P*-value are given in the box.

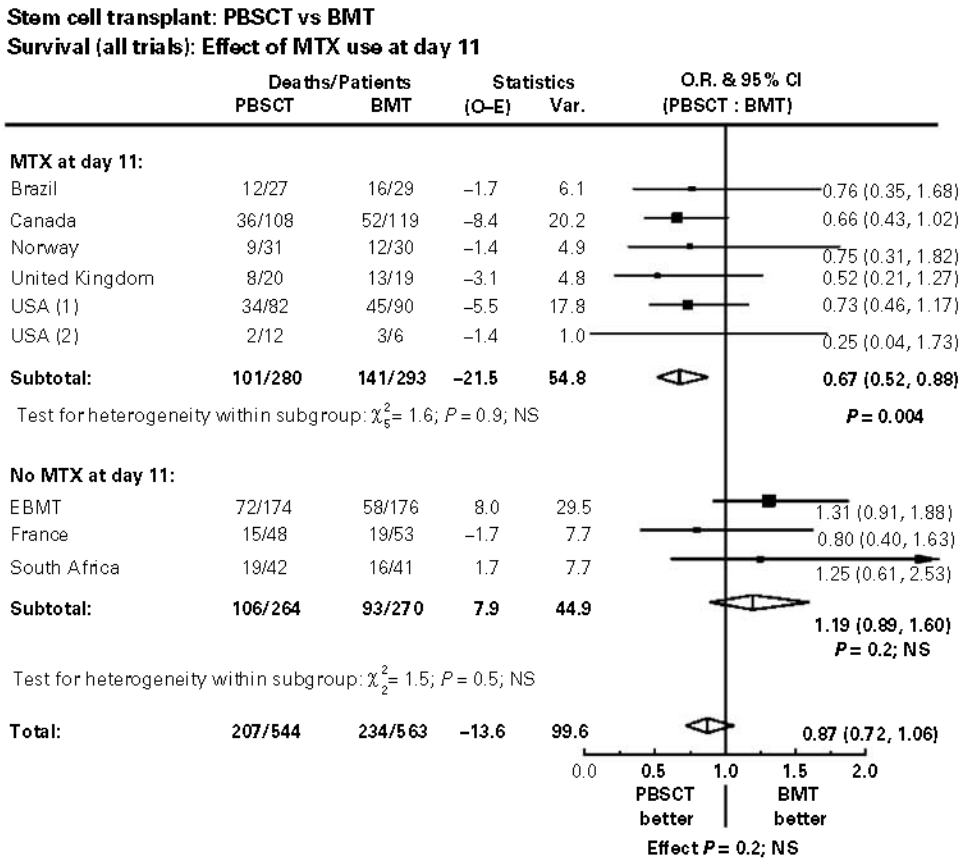

Figure 4.

Summary forest plots of survival demonstrating the interaction of day 11 MTX on outcomes. Tests for heterogeneity between MTX and no MTX groups were significant for survival.

Table 1

General characteristics of the randomized clinical trials that compared PBSCT versus BMT for the treatment of hematological malignancies

Trial (reference) (no.)	*Eligibility criteria*	*GVHD prophylaxis*[a]	*Patients characteristics*	*Disease*	*Risk categories*[b]	
					Favorable	*Unfavorable*
Saudi Arabia (unpublished) (N = 83)	Age 15–50 Hematologic malignancies Donor HLA = sibling	CSA/MTX (D +1,3,6)	Median age (range): 23 (15–48) Males (%):45 (54.2%)	ALL = 18 AML = 29 CML = 28 MDS = 8	42	39
France (13) (*N* = 101)	Age <55 years ALL, AML and CML (1st chronic phase), Donor HLA = sibling	CSA/MTX (D +1,3,6)	Median age (range): 36 (16–53) Males (%):53 (52.5%)	ALL = 19 AML = 45 CML = 37 MDS = 0	95	6
EBMT (12) (*N* = 350)	Age 16–55 years De novo AML and ALL (in 1st or 2nd remission or in 1st incipient relapse), CML (in chronic or accelerate phase), MDS (except RAEBT) Donor HLA = sibling	CSA/MTX (D +1,3,6)	Median age (range): 38 (17–58) Males (%):196 (56.0%)	ALL = 61 AML = 126 CML = 152 MDS = 11	301	38
Brazil (10) (*N* = 56)	Age 10–60 years Hematological malignancies Donor HLA = sibling	CSA/MTX (D +1,3,6,11) or CSA/PRED (3 pts at BMT arm)	Median age (range): 31 (7–60) Males (%):38 (67.8%)	ALL = 5 AML = 11 CML = 31 MDS = 5 Others = 4	37	19
Canada (11) (*N* = 228)	Age 16–65 years CML (in chronic or accelerate phase), AML (in remission) and MDS Donor HLA = sibling	CSA/MTX (D +1,3,6,11)	Median age (range): 45 (19–65) Males (%):133 (58.3%)	ALL = 0 AML = 83 CML = 109 MDS = 36	169	53
Norway (15) (*N* = 61)	Age 15–60 years AML, ALL, CML, PMF and MDS Donor HLA = sibling or one mismatched family donor	CSA/MTX (D +1,3,6,11)	Median age (range): 42 (15–55) Males (%):38 (62.3%)	ALL = 8 AML = 24 CML = 26 MDS = 1 Others = 2	42	12
UK (17) (*N* = 39)	Age 15–55 years Any hematological malignancies Donor HLA = sibling	CSA/MTX (D +1,3,6,11)	Median age (range): 37 (22–52) Males (%):29 (74.3%)	ALL = 7 AML = 13 CML = 12 MDS = 2 Others = 5	23	16
US1 (18) (*N* = 176)	Age 12–55 years Hematological malignancies Donor HLA = sibling	CSA/MTX (D +1,3,6,11)	Median age (range): 42 (12–56)	ALL = 22 AML = 39 CML = 58	86	89

Trial (reference) (no.)	*Eligibility criteria*	*GVHD prophylaxis*[a]	*Patients characteristics*	*Disease*	*Risk categories*[b]	
					Favorable	*Unfavorable*
US2 (28)[c] (*N* = 18)	CML Donor HLA = sibling	CSA/MTX (D +1,3,6,11)	Males (%): 122 (69.3%) Median age (range): 46 (19–61) Males (%):12 (66.7%)	MDS = 16 Others = 39 CML = 18	14	4

Abbreviations: ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; BMT = bone marrow transplantation; Bu = busulfan; CML = chronic myeloid leukemia; CSA = cyclosporine A; Cy = cyclophosphamide; GVHD = graft-versus-host disease; MDS = myelodysplastic syndrome; MTX = methotrexate; NHL = non-hodgkin lymphoma; PBST = peripheral blood stem cell transplantation; PMF = primary myelofibrosis; Pred = prednisone; RAEBT = refractory anemia with excess blast in transformation; TBI = total body irradiation.

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

[b]Risk categorization was unavailable for 19 patients.

[c]Seventy-two patients were included in this report, the majority of whom were in reference.[18]

Distribution of favorable/unfavorable groups: favorable ('good' prognosis): (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)).

Unfavorable ('poor' prognosis): (CML in second chronic phase, accelerated phase or blast crisis; AML or ALL, refractory or in >first remission; refractory anemia with excess blasts or in transformation subtypes of MDS, multiple myeloma, Hodgkin's disease, non-Hodgkin's lymphoma, and idiopathic myelofibrosis).