

CORRESPONDENCE

Multinomial Phase II Trial Designs

To the Editor: In the February 1, 2001, issue of the *Journal of Clinical Oncology*, Dent et al¹ described a phase II trial design that uses early progression in addition to objective response in its decision rules, the goal being to improve the efficiency of standard two-stage designs. We would like to clarify several issues concerning the statistical properties of this approach and its applicability to the testing of various types of agents.

Phase II trials are typically designed to test the null hypothesis (H_0) that the drug is inactive versus the alternative hypothesis (H_A) of promising activity. In terms of the true response rate, p_r , and the true early progression rate, p_p , Dent et al¹ defined H_0 as $p_r \leq p_{0r}$ and $p_p \geq p_{0p}$ and H_A as $p_r \geq p_{Ar}$ or $p_p \leq p_{Ap}$, where p_{0r} and p_{Ar} are the disappointing and promising response rates and p_{0p} and p_{Ap} are the disappointing and promising progression rates. With H_A defined in this manner with *or*, the alternative hypothesis includes points like $p_r = 0$ and $p_p = p_{Ap}$, and the multinomial stopping rules described in the article do not have the stated false-negative error rate. To illustrate this point, we tabulated the false-negative error rates of the first design given in Table 1 of Dent et al under several parameter values in H_A .

Our Table 1 shows that if H_A is defined as $p_r \geq p_{Ar}$ or $p_p \leq p_{Ap}$, the false-negative rate for the proposed rule is 100% and the rule is inappropriate. For the original motivation of the design, ie, utilization of early progression to allow efficient screening of inactive cytotoxic agents, a different alternative hypothesis, defined as $p_r \geq p_{Ar}$ and $p_p \leq p_{Ap}$, is more appropriate. Indeed, for this different alternative hypothesis, the false-positive and false-negative error rates stated in the article hold.

The second point we would like to clarify relates to application of the design to novel drugs that do not have standard cytotoxic mechanisms of action. It has been suggested^{1,2} that variations of this type of design can be used for evaluation of cytostatic drugs. It is important to understand that such variations are not simple and will require a nontrivial readjustment of the rules. The cytostatic setting, where either low progression rate or promising response rate is of interest, is more accurately described by the alternative hypothesis H_A ($p_r \geq p_{Ar}$ or $p_p \leq p_{Ap}$). Unfortunately, as we have just shown, the decision rules¹ do not have acceptable false-negative error rates against alternative H_A . Therefore, promising cytostatic drugs can potentially be rejected, eg, a drug with a true progression-free rate of 90% (see the penultimate line of our Table 1). In fact, the decision rule corresponding to our Table 1 terminates the trial after the first stage if no responses are seen even if none of the patients in the first stage progresses. In theory, decision rules using response and progression can be modified for cytostatic agents to increase sensitivity to a specific region in the alternative hypothesis, at a cost of loss of power in other regions. Such modifications will require a thorough assessment of the design performance over the range of possible progression and response rate values.

Besides cytostatic agents, nontraditional cytotoxic agents also include a number of recently developed agents aimed at specific molecular targets, eg, HER2 overexpression. Activity of such an agent depends on tumor cells expressing the target. Since in some cases reliable methods for identification of patients who express a sufficient amount of the target have not been developed, phase II trials of these agents are sometimes performed with patients regardless of their expression status. In this setting, it might not be unusual for a small proportion of patients (who express a sufficient amount of the target) to

Table 1. False-Negative Error Rates

True p_r, p_p	Probability of Declaring Drug Inactive
.2, .4	.19
.2, .6	.58
.05, .4	.70
.25, .6	.43
.05, .3	.57
0, .1	1
.2, .8	.65

NOTE. This table shows the false-negative error rates (probability of accepting H_0) for the decision rule in Table 1 of Dent et al,¹ which uses disappointing values of $p_{0r} = .05$ and $p_{0p} = .6$ and promising values of $p_{Ar} = .2$ and $p_{Ap} = .4$.

have a very good response while the other patients progress rapidly. The trial designs,¹ which were validated with data from trials of standard cytotoxic agents, may have poor properties in this situation, eg, the last line of our Table 1.

We believe that elucidation of these issues will enhance and promote the correct application of these designs by the clinical research community.

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Intravenous Immunoglobulin for Hemophagocytic Lymphohistiocytosis?

To the Editor: On the basis of a retrospective analysis of 47 children and young adults, Imashuku et al¹ conclude that early (< 4 weeks from diagnosis) administration of etoposide, preferably with cyclosporin A, is the treatment of choice for patients with Epstein-Barr virus (EBV)-associated hemophagocytic lymphohistiocytosis (HLH). On the other hand, they show data which "indicate that [intravenous immunoglob-

ulin (IVIG)-based primary regimens may not be adequate for most patients with EBV-HLH.”

Conversely, we and others have evidence that IVIG is effective in the treatment of HLH.^{2,3} What are the reasons for this opposite conclusion? First, the patients analyzed are not the same, particularly regarding age (children and young adults with a median age around 5 years in Imashuku et al and adults with a median age of 35 and 41 years in Larroche et al³ and our series,² respectively), selection criteria (based on the diagnostic guidelines of the Histiocytic Society, adapted by Imashuku et al,⁴ not further specified in Larroche et al, and mainly based on serum hyperferritinemia $\geq 10,000$ $\mu\text{g/L}$ and/or demonstration of hemophagocytosis in our series), and underlying diseases. Second, serum ferritin values tend to be lower in the patients of Imashuku et al, which might point to a lower disease activity⁵ or possibly reflect ferritin measurements some time after the peak macrophage activation. Third, EBV-HLH seems to be more prevalent in Asiatic populations (though a publication bias cannot be excluded), which suggests genetic influences. The genetic background may influence response to treatment as well.

A key finding of our analysis is the efficacy of IVIG if it is administered at the beginning (within hours) of the macrophage activation process and its failure in later stages of the disease.³ Serum ferritin seems to be a useful emergency marker for monitoring macrophage activation. It is possible that IVIG was administered too late in the patients described by Imashuku et al.¹ In addition, the patients who profit most from the administration of IVIG have yet to be defined in more detail. For instance, lymphoma-associated HLH is less responsive to IVIG than some other forms (Larroche et al³ and our own unpublished observations). A prospective, randomized trial that is about to start should clarify these questions. Furthermore, the recently described rabbit model of EBV-HLH might allow for the testing of different treatment strategies.⁶

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In Reply: We thank Dr Emmenegger and colleagues for their important remarks about our article on Epstein-Barr virus (EBV)-associated hemophagocytic lymphohistiocytosis (HLH).¹ Our conclusion that etoposide rather than intravenous immunoglobulin (IVIG) is important in the treatment of EBV-HLH was based on the 10 patients listed in Table 2, who did not respond sufficiently to regimens that included IVIG but did subsequently improve with etoposide-based regimens. Similar observations are available in previously published Japanese articles, although mostly as case reports. In addition, our analysis clearly showed that therapeutic results were better for patients who received etoposide early (< 4 week from diagnosis) in their treatment course.

As we cited in our article, reports on the beneficial effect of IVIG in patients with hemophagocytic syndrome have been accumulated. In article by Larroche et al² reporting IVIG effectiveness, all 17 cases were non-EBV infection-associated HLH (non-EBV-HLH) or were triggered by other causes. We agree that IVIG is effective for patients with non-EBV-HLH. The reason why EBV-HLH did not respond well enough to IVIG in our study remains to be determined. We think that the first and second issues raised by Emmenegger et al are unlikely, as they explain different IVIG effectiveness between their study and ours. In terms of genetic influences, Beutel et al³ very recently compared the EBV-HLH in German children with that reported from Japan. They observed similar biochemical markers, such as hypercytokinemia and high ferritin and lactate dehydrogenase levels; however, they could not find the hypocellularity and increased large granular lymphocytes in the bone marrow described for Japanese patients.⁴ In addition, they noted a high proportion of mild clinical courses in Germany, which is different from the reports in Asia.

We assume that the EBV-HLH or EBV-related macrophage activation syndrome is distinct from non-EBV-HLH, because the majority of EBV-HLH is a clonal disease. In fact, approximately 90% of the EBV-HLH we studied was confirmed to be mono- or oligoclonal (tested by a terminal probe for EBV), and 60% showed T-cell receptor rearrangements.⁵ These results suggest that EBV-HLH resides in a gray zone between infectious disease and lymphomatous disease.⁶ Although clonal disease does not necessarily indicate malignant neoplastic disease, our observation could be compatible with Emmenegger et al's comments that lymphoma-associated HLH is less responsive to IVIG. In this setting, we must be careful in using the term "reactive hemophagocytic syndrome." Because hemophagocytosis itself is reactive, the disease may have been triggered by nonclonally or clonally proliferating lymphocytes or true neoplastic cells. It is possible that IVIG modulates hemophagocytosis due to hypercytokinemia, but it may not suppress the growth of the underlying clonally proliferating cells like in EBV-HLH. We agree that further studies are necessary to find out the most optimal treatment for EBV-HLH, although our study con-

firmed the superiority of etoposide over IVIG for this often fatal disease.

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Management of Anemia in Patients Receiving Chemotherapy

To the Editor: We congratulate Littlewood et al on their randomized trial of epoetin alfa versus placebo in patients receiving nonplatinum-based chemotherapy for advanced solid tumors, reported in the June 1, 2001, issue of the *Journal of Clinical Oncology*.¹ Their study demonstrates a reduction in transfusion requirements and improved quality of

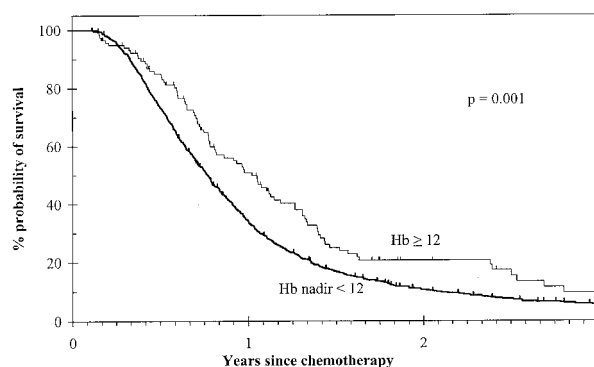


Fig 1. Kaplan-Meier survival curves for 906 patients treated with chemotherapy for small-cell or non-small-cell lung cancer according to lowest recorded hemoglobin (Hb) level during treatment.

life for patients randomized to receive epoetin alfa. Intriguingly, they also show a trend to improved survival for this group of patients, although the trial was not powered to examine this end point. Regardless of how this article will change clinical practice, it also suggests that our current definition of anemia in cancer patients should be re-evaluated.

Our current level of hemoglobin that triggers transfusion or intervention (generally < 10 g/dL) may not be optimal. Using a hemoglobin level of 12 g/dL as a cutoff for anemia, we have examined the association between the lowest recorded hemoglobin level and survival among patients receiving chemotherapy for small-cell and non-small-cell lung cancer treated at Royal Marsden Hospital between 1990 and 2001. Anemia was very common, with 86% of the 906 patients studied experiencing a nadir hemoglobin level lower than 12 g/dL at any time during chemotherapy treatment or within 1 month of completing chemotherapy. Survival rates for patients who maintained their hemoglobin levels above 12 g/dL throughout treatment were significantly better than rates for those whose nadir hemoglobin was below this level (median survival, 12 months v 9 months, respectively; $P = .001$) (Fig 1). This survival difference was maintained after adjustment for the major prognostic factors of tumor stage and performance status.

These retrospective data generate the hypothesis that maintaining hemoglobin above 12 g/dL in the palliative setting could prolong life by as long as it is currently prolonged with palliative chemotherapy in non-small-cell lung cancer. The baseline hemoglobin level has been shown to have independent prognostic significance in patients receiving radiotherapy for this disease in some studies,² although in others its significance was lost after multivariate analysis.³ Thus, an alternative explanation for these data is that hemoglobin level may just be another prognostic factor independent of performance status and stage, not previously rigorously sought, that reflects the biology of the tumor. Even if this is the case, it is a prognostic factor that could be modified and improved upon and is therefore worth investigating. These data support the evaluation of epoetin alfa in a randomized trial powered to detect a survival benefit that may be of a similar magnitude to that produced by palliative chemotherapy for these diseases. Further interesting trials would examine whether an additional therapeutic benefit over

current treatments may accrue from the maintenance of hemoglobin above 12 g/dL by whatever means.

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In Reply: We thank Waters et al for their insightful and informative remarks. They have highlighted both the importance of hemoglobin (Hb) levels with respect to therapeutic outcome in cancer patients and the multiple benefits that may accrue with administration of epoetin alfa to increase Hb levels in anemic cancer patients.

The results of our study,¹ as well as those of three large, community-based trials in over 7,000 patients,²⁻⁴ have demonstrated that epoetin alfa therapy significantly increases Hb levels in anemic cancer patients, with subsequent improvement in a number of quality-of-life (QOL) domains known to be negatively impacted by cancer-related anemia (Cancer Linear Analog Scale/Linear Analog Scale Assessment: energy level, ability to do daily activities, and overall QOL subscales; Functional Assessment of Cancer Therapy–Anemia: anemia subscale). Further, these studies provided data enabling our group and other investigators to determine the optimal target level for Hb, ie, that level which will result in the greatest incremental gain in QOL. In a marginal analysis of data from each of the aforementioned community-based studies, the greatest incremental gains in QOL were found to have occurred when Hb levels increased from 11 to 12 g/dL (range, 11 to 13 g/dL).²⁻⁵ Similarly, an incremental analysis of data from our own placebo-controlled study showed that the greatest positive changes in QOL were associated with a final Hb level of approximately 13 g/dL.⁶ QOL continued to improve as Hb increased to 14 g/dL but at a slower rate. Together, the results of these analyses suggest that a target level of 12 to 13 g/dL will produce the greatest gains in QOL and that treatment of anemia should therefore begin well before the Hb level decreases dramatically below 10 g/dL.

Interestingly, Hb levels in the 12- to 13-g/dL range also seem to be important for patients' response to cancer therapy and overall survival. In their letter, Waters et al noted that a retrospective review of data for lung cancer patients treated at their institution over the last decade showed better survival rates for patients with nadir Hb levels above 12 g/dL throughout chemotherapy, compared with those whose nadir Hb levels were below this level. This observation is consistent with the findings of other studies, which suggest that anemia in cancer patients may lead to poor tolerance of chemotherapy and radiation therapy, decreased locoregional tumor control, and decreased survival time.⁷ In a retrospective study, long-term outcomes were evaluated for patients

who received radiotherapy for squamous cell tumors of the head and neck. In this study, the estimated 5-year survival rate for patients with Hb levels ≥ 13 g/dL for men and ≥ 12 g/dL for women was 58%, compared with 28% for patients with Hb levels below these respective values.⁸ Also, significantly higher rates of overall relapse, local recurrence, and distant metastases have been reported for patients with average weekly nadir Hb levels of less than 12 g/dL during radiotherapy, compared with patients whose average weekly nadir Hb levels were ≥ 12 g/dL.⁹

These findings and those of earlier investigators have prompted efforts to correct low Hb levels in anemic cancer patients, with the goal of improving therapeutic outcome. One option for doing this has been transfusion of RBCs. However, as demonstrated in our study, although transfusions can stabilize Hb levels, they can not prevent deterioration of QOL and may fail to provide any survival benefit (our study showed a trend in overall survival favoring epoetin alfa over placebo, although the study was not powered for survival as an end point¹). In contrast, a growing body of evidence indicates that epoetin alfa therapy, by increasing Hb levels, may provide a survival benefit in addition to improving QOL. In a study in patients receiving chemoradiation for squamous cell carcinoma of the oral cavity and oropharynx, Glaser et al¹⁰ found significantly higher response, locoregional control, and survival rates in patients with pretreatment Hb of ≥ 14.5 g/dL or less than 14.5 g/dL given epoetin alfa, compared with patients with levels less than 14.5 g/dL not given epoetin alfa.¹⁰

Additional evidence of a survival benefit with epoetin alfa is emerging from studies in animal models. In a recently reported preclinical study, Mittelman et al¹¹ evaluated the biologic effects of epoetin alfa on the course of tumor progression, using murine myeloma models. In one model (MOPC-315-IgA λ_2), daily treatment with epoetin alfa induced complete and permanent tumor regression in 30% to 60% of mice, an effect that was shown to be attributable to a T-cell-mediated mechanism. The investigators indicated that erythropoietin may have an intrinsic antitumor effect in addition to its RBC-stimulating activity.

In summary, there is now convincing evidence that Hb may be an independent prognostic factor for treatment outcomes, as alluded to by Waters et al, and that treating cancer-related anemia with epoetin alfa can provide multiple benefits for patients, including improved QOL, and, possibly, increased survival time. However, further study is necessary to more fully explore and define the potential of this agent.

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Chronic Graft-Versus-Host Disease After Allogeneic Peripheral-Blood Stem-Cell Transplantation: A Little Methotrexate Goes a Long Way

To the Editor: Cutler et al¹ are to be commended for their attempt to answer the question of whether the incidence of chronic graft-versus-host disease (GVHD) is increased with the use of allogeneic peripheral-blood stem-cell transplantation (PBSCT) as an alternative to bone marrow transplantation (BMT) through a meta-analysis. However, we are not certain that their conclusion—that the incidence of chronic GVHD is higher after PBSCT—is entirely accurate. Their analysis did not take into account the one critical factor likely to affect the development of GVHD, the GVHD prophylaxis regimen.

We strongly believe that methotrexate not only is a critical component of a standard GVHD prophylaxis regimen (cyclosporine or tacrolimus with methotrexate 15 mg/m² on day 1 and 10 mg/m² on days 3, 6, and 11) but also has to be delivered in a rigorous fashion (all scheduled doses) to be effective.² The two prospective studies^{2,3} that did not show a significant increase in chronic GVHD and showed lower relapse and better disease-free survival used the standard methotrexate-containing regimen. All patients in both studies received all the doses of methotrexate. Growth factors were not administered routinely in either study.

Table 1. GVHD Prophylaxis and Posttransplant Growth Factor Administration in Studies of GVHD Prophylaxis

Study (ref)	Suboptimal Methotrexate	Posttransplant Growth Factor
Bacigalupo ⁵	No	No
Blaise ⁶	Yes (no methotrexate on day 11)	No
Lemoli ⁷	No	No
Russell ⁸	No	No
Schmitz ^{9,10}	Yes (no methotrexate on day 11)	Yes
Scott ¹¹	Nonstandard (8 mg/m ² on days 2, 4, 8, and 12)	Not specified
Solano ¹²	Yes (no methotrexate on day 11 in 54% of PBSCT recipients and 24% of BMT recipients; <i>P</i> = .017)	Yes
Ustun ¹³	No	No
Vigorito ¹⁴	Not specified	No

Support for our belief that methotrexate is important² comes from a recent retrospective study showing that methotrexate-containing GVHD prophylaxis was associated with a significantly lower risk of extensive chronic GVHD (risk ratio, 0.35; 95% confidence interval, 0.2 to 0.6; *P* = .001).⁴ As described by Przepiorka et al,⁴ the patients who received tacrolimus-methotrexate GVHD prophylaxis without getting inordinately high doses of CD34⁺ cells had an actuarial risk of chronic GVHD of 51%, which is comparable to that described by Bensinger et al³ and by us.²

Table 1 shows some of the studies cited by Cutler et al.¹ Two^{8,13} of the four studies that seemed to have used standard methotrexate-containing prophylaxis found an increase in chronic GVHD, whereas two did not.^{5,7} The two that did show increased chronic GVHD^{8,13} did not specify whether all four doses of methotrexate were delivered to PBSCT recipients or whether modifications/omissions were made on account of factors such as mucositis. All five studies that used, according to us, suboptimal GVHD prophylaxis^{6,9-12} or that did not provide details of methotrexate administration¹⁴ showed increased chronic GVHD after PBSCT. The European Blood and Marrow Transplant Group study^{9,10} also used routine granulocyte colony-stimulating factor after transplantation—another potential confounding factor in assessing outcome.

The significantly higher numbers of T cells infused during PBSCT¹⁻¹⁵ may mean that alterations in methotrexate dosing and schedules have more profound effects after PBSCT than after BMT. Other than reduced relapse, the higher number of CD34 cells infused (although not excessively so) with PBSCT could translate into decreased treatment-related mortality.¹⁵ On the basis of our experience¹⁵ and the data from Przepiorka et al showing increased acute¹⁶ and chronic⁴ GVHD with very high CD34⁺ cell doses, we infuse between 3 and 5 × 10⁶ CD34⁺ cells/kg recipient body weight.

Is there a place for yet another randomized study of BMT and PBSCT? Probably not, not the least because it may be considered unacceptable to perform BMT if PBSCT is possible under optimized clinical conditions. However, it may be worthwhile to study GVHD prophylaxis after PBSCT to see whether the outcome can be improved any further. The comparisons could be standard cyclosporine-methotrexate versus cyclosporine-methotrexate and mycophenolate mofetil or cyclosporine-methotrexate followed by a standard taper

(from day 50 to 180) versus an extended taper (eg, from day 100 to 270).

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In Reply: Drs. Mehta and Singhal are correct in pointing out that several important contributing factors influence the development of graft-versus-host-disease (GVHD) after either peripheral-blood stem-cell transplantation (PBSCT) or bone marrow transplantation (BMT). One of the best characterized risk factors for the development of GVHD is the omission of an effective GVHD prophylaxis regimen that includes methotrexate.¹ Despite the lack of uniformity in methotrexate regimens in our analysis, we believe the results to be valid for several reasons.

Methotrexate can be given according to several different regimens. However, the schedule of 15 mg/m² on day +1 and 10 mg/m² on days +3, +6, and +11 remains the standard after allogeneic transplantation. It is to be noted that this regimen was adopted by the transplant community without the benefit of a randomized trial examining the optimal duration or timing of therapy.

In our original report,² six trials utilized the standard dose schedule.³⁻⁹ Mehta and Singhal summarize the methotrexate regimens used in some of the trials in their table. However, they misrepresent the trial reported by Bacigalupo et al,¹⁰ in which methotrexate was used according to a nonstandard regimen (15 mg/m² on day +1 and 8 mg/m² on days +3 and +6), and the trial reported by Vigorito et al,⁹ in which methotrexate was used according to the standard dose schedule (C. de Souza, personal communication, 2001). Two of the trials that used the standard dose schedule demonstrated a significant increase in the risk of chronic GVHD (relative risk [RR], 1.76 and 95% confidence interval [CI], 1.26 to 2.46^{6,7}; RR, 3.65 and 95% CI, 1.75 to 7.58⁸), while the four other studies all demonstrated trends favoring a higher incidence of chronic GVHD after PBSCT (RR range, 1.19 to 1.52, *P* = not significant).^{3-5,9} Of the five prospective randomized trials included in our original analysis, three utilized standard-dose methotrexate as GVHD prophylaxis^{3,5,9} while the two other trials used abbreviated courses.¹¹⁻¹³ One of the trials using abbreviated methotrexate independently demonstrated a statistically significant increase in chronic GVHD (RR, 1.82 and 95% CI, 1.10 to 3.00),¹¹ while all four others demonstrated a trend toward increased chronic GVHD after PBSCT (RR range, 1.19 to 1.52, *P* = not significant).^{3,5,9,12,13} Of note, a more recently published randomized trial demonstrated a significantly increased rate of chronic GVHD despite full-dose methotrexate,¹⁴ while a trend toward increased chronic GVHD was demonstrated in another trial published in abstract format that also used standard-dose methotrexate.¹⁵

Kumar et al¹⁶ have demonstrated that omission of the day +11 dose of methotrexate after allogeneic BMT did not increase the rate of chronic GVHD in a retrospective study of 123 patients (39% v 37%,

$P = .87$).¹⁶ In order to determine whether the RR increase in chronic GVHD was due to differences in methotrexate delivery as part of GVHD prophylaxis regimens, we compared RR results from separate meta-analyses stratified by methotrexate regimen. In the trials that used standard-dose methotrexate,³⁻⁹ the RR of chronic GVHD after PBSCT when compared with BMT was 1.60 (95% CI, 1.19 to 2.13, $P = .002$). In trials in which the day +11 methotrexate was omitted in some¹⁷ or all of the patients¹¹⁻¹³ or in which alternate dosing schedules of methotrexate were used,^{10,18} the RR of chronic GVHD after PBSCT compared with BMT was 1.49 (95% CI, 1.03 to 2.17, $P = .036$). These results are not statistically different ($P = .76$). The trials in which multiple GVHD prophylaxis regimens were used were omitted for this analysis.¹⁹⁻²²

In the retrospective analysis recently published by Przepiorka et al,¹ methotrexate-containing regimens were associated with a lower incidence of chronic GVHD. However, the delivered doses of methotrexate were not determined retrospectively. Furthermore, methotrexate was used in combination with tacrolimus rather than cyclosporine, and this newer combination may be more effective for prevention of GVHD in both the related and unrelated setting.^{23,24} Within the individual trials we examined, PBSCT and BMT groups received similar GVHD prophylaxis regimens composed of cyclosporine and methotrexate. Because differential or incremental benefits of increased doses of methotrexate have not been demonstrated to exist between peripheral-blood stem-cell or bone marrow grafts despite increased CD3⁺ and CD34⁺ cell counts with peripheral-blood stem cells, we felt it was appropriate to pool the relative risks from the individual trials in the meta-analysis.

Individual trials are often underpowered to detect small changes in GVHD outcome. Thirteen of the 14 trials we examined showed evidence of increased chronic GVHD after PBSCT when compared with BMT. However, only a few were able to independently demonstrate this statistically. The findings from our meta-analysis support the notion that the incidence of chronic GVHD is greater after PBSCT when compared with BMT.

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