Critical Factors in Optimizing Graft-Versus-Leukemia Effect for Relapsed Leukemias

To the Editor: Graft-versus-host disease has been shown to reduce the risk of relapse for acute leukemias, both lymphoid and myeloid, after an allogeneic transplantation, but donor lymphocyte infusion (DLI) is rarely effective in curing relapsed acute leukemias. One explanation for this phenomenon is the rapid progression of acute leukemias and accelerated chronic myeloid leukemia (CML). Chemo-thapy alone is not effective in achieving a long-term cure in patients with these diseases. The approach used by Levine et al is probably the most rational one in that it uses cytoreduction before DLI.

However, this approach failed to improve the disease-free or overall survival significantly. Graft-versus-host disease was associated with worse outcome and did not translate to a graft-versus-leukemia (GVL) effect. Given these findings, it would be tempting to hypothesise that the GVL effect does not cure relapsed leukemias. However, there are a few issues that need to be addressed in order to optimize the GVL effect.

The concept of using mobilized DLI after chemotherapy is the same as a nonmyeloablative transplant. In that context, the timing of the DLI is probably critical. Bacigalupo et al reported that the impact of low-dose cyclosporine in reducing the relapse risk was in the first 10 days after transplantation. This is probably the period of maximal cytopenia and is the right milieu for the proliferation of donor effector cells with minimal or no competitive effect of host lymphocytes. Levine et al used DLI 10 to 14 days after the chemotherapy, which is not within this critical time period. On the basis of this observation, DLI should probably be scheduled within the first 3 days after chemotherapy, in accordance with the same principle as in a transplant procedure.

One study suggested that patients with a greater burden of host lymphocytes respond less well to DLI. This concept is bolstered by the observation that after immunosuppression-based reduced-intensity conditioning, remission is achieved faster in CML patients than it is usually after DLI alone, and conversion to full donor chimerism in the T-cell lineage precedes a GVL response. Levine et al did not clarify how many patients received purine analog–based regimens and whether that influenced the outcome. There is probably a rationale for using purine analogs or other immunosuppressive drugs in the pre-DLI chemotherapy regimen to eliminate host lymphocytes that might impair the alloreactivity of donor lymphocytes by inducing tolerance.

This brings in the question of T-cell chimerism and efficacy of DLI. Our limited experience with lineage-specific chimerism following both conventional and reduced-intensity transplantation suggests that donor T-cell engraftment lags behind granulocyte chimerism, which is often not picked up on chimerism analysis of whole blood or marrow. It would have been interesting to study the lineage-specific chimerism in relation to remission in the report by Levine et al.

The final point we would like to highlight is that granulocyte colony-stimulating factor (CSF)-mobilized apheresis products might be important in preventing post-DLI aplasia, but the present body of literature suggests that granulocyte CSF might have a negative effect on alloreactivity. The use of granulocyte-macrophage CSF in mobilization, both before and after DLI, needs to be explored in an attempt to improve antigen presentation to the effector cells and improve the GVL effect.

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REFERENCES


In Reply: Dr Chakrabarti notes that acute leukemia relapse rates in adults were lower when less immunosuppression was given in the first 10 days after myeloablative transplantation. Recipients of lower-dose immunosuppression who were younger than 30 years had superior survival, but this benefit did not hold true for patients older than 30 years. On the basis of this observation, Chakrabarti speculates that the optimal time to achieve the graft-versus-leukemia (GVL) effect is to administer donor lymphocyte infusion (DLI) earlier than the 10 to 14 days following chemotherapy, as was performed in our study. However, earlier administration of DLI may increase the risk of graft-versus-host disease (GVHD) unless postinfusion immunosuppression is provided. In a myeloablative murine model, Xun et al showed that delaying T-cell infusion from day 0 to day 4 after total-body irradiation (TBI) led to a substantial reduction in GVHD-related mortality. Conditioning-related tissue damage and subsequent inflammatory cytokine release might be important mechanisms for the risk of lethal GVHD after T-cell infusion. Although Chakrabarti puts forth an interesting hypothesis, further study will be needed to determine whether an earlier DLI will result in a greater GVL effect, worse GVHD, both, or neither.
Chakrabarti interprets the failure to observe a survival benefit of GVHD after DLI in our study to mean that a GVL effect was not operative. This is not necessarily true. Horowitz et al. showed that the GVL effect need not occur in the context of clinically evident GVHD. However, in the absence of a randomized comparison, we make no claim of superiority of our approach over any other. For example, Pawson et al. recently reported overall survival of 60% and disease-free survival of 28% at 58 months after a second nonmyeloablative transplant for acute leukemia relapse following a failed first allogeneic transplant. We believe that further investigation into inducing meaningful GVL effects while minimizing regimen-related and GVHD-related mortality is warranted for patients with advanced myeloid leukemia relapse after allogeneic stem-cell transplantation.

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**REFERENCES**


3. Xun CQ, Tschida M, Thompson JS: Delaying transplantation after total body irradiation is a simple and effective way to reduce acute graft-versus-host disease mortality after major H2 incompatible transplantation. Transplantation 64:297-302, 1997


**Statistical Explanations for a Community-Based Study of Once-Weekly Epoetin Alfa Therapy in Patients Receiving Chemotherapy**

To the Editor: Drs Nguyen and Trinh have raised a number of statistical issues with regard to our recently published, open-label, nonrandomized study of once-weekly (QW) epoetin alfa therapy in anemic patients receiving chemotherapy for nonmyeloid malignancy. Because their comments were of a technical nature, the input of the statistical analysis group (Analysis Group/Economics, Cambridge, MA) was sought. Here we provide point-by-point responses to the statistical shortcomings that were proposed.

In the published article, we concluded that the hematopoietic and quality-of-life (QOL) benefits of QW epoetin alfa therapy—as determined by hemoglobin levels, transfusion requirements, linear analog scale assessment (energy level, ability to perform daily activities, and overall quality of life), and the anemia subscale of the Functional Assessment of Cancer Therapy—Anemia (FACT-An) questionnaire—appeared to be similar to those documented in Demetri et al.’s community-based study of three-times-weekly (TIW) dosing. Both studies involved nonmyeloid cancer patients with anemia (defined as a hemoglobin level of 11 g/dL or less) who were undergoing concomitant chemotherapy in community-based practice. Nguyen and Trinh noted that differences between the studies, particularly regarding baseline patient characteristics, hemoglobin level increases, and changes in QOL, were not formally analyzed. Although these data were not reported, the patient populations indeed had similar baseline demographic and disease characteristics. While some outcomes are statistically different, none appear to be clinically meaningful. For example, the average baseline hemoglobin level among patients receiving TIW therapy was 9.3 g/dL versus 9.5 g/dL in the QW population (P < .05). Similarly, the mean anemia subscale of the FACT-An score was 41.4 among patients receiving TIW therapy versus 42.5 for QW therapy. These differences are statistically significant because of the large samples, but they are not clinically meaningful. With respect to the lack of formal hemoglobin and QOL analyses, it is important to recognize our use of a difference-in-difference approach, which is less sensitive to baseline differences between the study populations. As a result, our conclusions regarding the effectiveness of QW versus TIW epoetin alfa therapy were based on whether the change in hemoglobin level or QOL with QW dosing was different from what it was with TIW administration—not whether the final hemoglobin level was the same in the two studies (in this case, baseline would matter). This difference-in-difference approach is mathematically equivalent to a fixed-effects method and greatly reduces the potential impact of differences in covariates across studies. This approach is commonly used in the analysis of longitudinal data.

A second criticism was that a random-effects model, which accounts for the variation in treatment effects across practices, would have been more appropriate than our fixed-effects method. Importantly, however, the use of a random-effects model in data analyses requires knowledge of the distribution of errors within and between each patient. Given that no such information was available, relying on a random-effects model may have biased our results. On the contrary, the fixed-effects method’s potential to reduce degrees of freedom was not a concern because the studies included thousands of observations. Overall, the fixed-effects method (which uses patients as their own controls) would result in unbiased and more efficient estimates compared with a random-effects model, and on this basis, we felt it was the most suitable analytic approach.

Other stated problems pertained to the data that were presented in the published figures, the first being an uncertainty regarding the number of assessable patients at study end point. A total of 1,745 patients completed epoetin alfa therapy (as stated in the text), whereas information on hemoglobin levels at week 16 was only available for 1,715 patients (as shown in the figures). Thus, the different patient numbers do not represent a discrepancy. Second, it was felt that the summary statistics for change in hemoglobin level, the percentage of patients requiring transfusion, and the number of units of blood transfused per patient (presented in Figs 1, 2, and 3, respectively) could be misleading, as the numbers of patients varied over time. Please note, however, that the number of assessable patients and the attrition are clearly indicated in each figure, limiting the risk of misinterpretation.

It was proposed that the mean increase in hemoglobin from baseline to study end point was inappropriately calculated via determination of the difference between the values (ie, 11.3 g/dL − 9.5 g/dL = 1.8 g/dL), despite the fact that the patient numbers were different. It is coincidental that the mean of individual patient differences and the...
difference in overall means are identical. The 1.8 ± 1.8 g/dL hemoglobin level increase reported for 2,869 patients is the mean change in individual patient changes in hemoglobin (± SD) rather than the difference of the means at baseline and at study end point. Because the mean increase in hemoglobin level was calculated via the last value carried forward approach (ie, each patient’s baseline and last available hemoglobin levels were used), the number of patients at baseline and at the end of the study are the same for the purpose of this test.

Lastly, according to Nguyen and Trinh, “under the assumption of normality, it can be inferred from the data that apart from the majority of patients whose hemoglobin levels had been improved, approximately 33% of patients had experienced either unchanged or decreased hemoglobin levels.” With a mean hemoglobin level change of 1.8 g/dL and a SD of 1.8 g/dL, only 16% of patients would experience a negative change under a normality assumption. From the data themselves, the proportion of patients with either unchanged or decreased hemoglobin levels from baseline to final evaluation is 17.8%, as would be expected.

Overall, we believe that our publication is statistically sound and supports the conclusion that QW and TIW dosing of epoetin alfa produce similar improvements in hemoglobin level, transfusion requirements, and self-perceived QOL among anemic cancer patients receiving concomitant chemotherapy.

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REFERENCES


Oxaliplatin: Bimonthly, Biweekly, or Semimonthly?

To the Editor: Oxaliplatin is a new anticancer drug active against colorectal cancer; it was developed mostly in France.1-3 The drug is usually given every 2 weeks. To describe their regimens, French authors have used the term “bimonthly.” This use of the word “bimonthly” has caused and continues to cause confusion in the English literature.

In French, the word “bimensuel” is not ambiguous and means “twice a month.” By contrast, in English the word “bimonthly” is ambiguous: Although it generally means “every 2 months,” it can also mean “twice a month.” Nevertheless, the latter meaning is seldom used in order to avoid confusion. Webster’s dictionary proposes to use the term “semimonthly” instead. Similarly, the French “biméridianaire” is not ambiguous and means “twice a week.” By contrast, the English “biweekly” generally means “every 2 weeks” but may also mean “twice a week.”

What is the best way out of this semantic confusion? Since “bimonthly” has the general meaning of every 2 months in current English, the term “bimonthly” should not be used to describe an every-2-weeks schedule. If authors prefer to refer to the duration of half a month (implying some imprecision, from 14 to 16 days) they should use the term “semimonthly.” If they prefer to refer to the duration of 2 weeks, they should use the term “biweekly,” implying precisely 14 days.

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REFERENCES


Association of Tamoxifen and Uterine Sarcoma

To the Editor: Over the last 20 years, tamoxifen has become an important component of treatment for both early and advanced hormone receptor–positive breast cancer. In the late 1990s, clinical trial findings reported by the National Surgical Adjuvant Breast and Bowel Project (NSABP) demonstrated the utility of tamoxifen in ductal carcinoma-in-situ1 and in risk reduction for women at high risk for developing breast cancer.2 A consistent finding in our trials has been an increased risk of developing uterine (endometrial) cancer in women taking tamoxifen,3 a risk that seems to increase the longer the drug is administered. The mechanism for this increased risk is thought to be the estrogen agonist activity of tamoxifen on the uterus, which is similar to the mechanism for increased incidence of uterine cancer in women who take unopposed estrogen as hormone replacement therapy.4,5

Uterine sarcoma is a rare form of uterine malignancy, occurring in 2% to 5% of all patients with uterine malignancy,6-7 with an incidence of approximately one to two cases per 100,000 women in the general population. Its signs and symptoms are similar to those of endometrial cancer. There are three general types of uterine sarcoma: malignant mixed mullerian tumors (MMMT, also known as malignant mixed mesodermal sarcoma or carcinosarcoma), which contain both epithelial and stromal elements (50%), and leiomyosarcomas (40%) and stromal cell sarcomas (10%), both of which lack epithelial elements. Whereas estrogens have been shown to play a causal role in the pathogenesis of endometrial adenocarcinomas, such a link has not been established for
uterine sarcomas in general, although it may exist for the MMMT variant.8-13 Although the prognosis for uterine sarcoma is primarily dependent on the stage and histology of the disease at the time of diagnosis, this malignancy, particularly the MMMT variant, tends to present at a more advanced stage and may carry a worse prognosis in terms of disease-free and overall survival.

In NSABP studies in which we categorized second malignancies according to organ site, we found a small number of uterine sarcomas (predominantly MMMT) among the endometrial cancers that occurred.1 It was unclear whether the incidence of these malignancies was increased in women taking tamoxifen. Because a recent case-control study14 has suggested that this may be the case, we updated data on the incidence of uterine malignancy that occurred in our patients and reviewed additional information from a Surveillance, Epidemiology, and End-Results (SEER)-based case-control study and from the manufacturer of tamoxifen, AstraZeneca (Wilmington, DE). Our aim was to further evaluate the possible association of tamoxifen use and an increased risk of uterine sarcoma.

In NSABP trials B-09, B-14, B-21, B-23, B-24, and P-1, more than 17,000 women were randomized to take tamoxifen or placebo (Table 1). The duration of treatment was 2 years in B-09 and 5 years in the other trials. On protocol B-14, patients who completed 5 years of tamoxifen had the option to be randomly assigned to receive either up to an additional 5 years of tamoxifen or placebo. The NSABP continues to obtain follow-up information on these patients, including data on the incidence of second malignancies, breast cancer recurrence and/or incidence, and survival.

Table 2 shows the incidence of uterine malignancy by treatment group and by histologic type (adenocarcinoma or sarcoma) in these studies as of September 30, 2001. From these data, it seems that the incidence of both common adenocarcinoma and uterine sarcoma is increased in women taking tamoxifen, with sarcomas making up approximately 10% of total uterine malignancies in these patients.

To examine this question further, staff at AstraZeneca reviewed all available data on tamoxifen in its global drug safety database through July 11, 2001, for the occurrence of uterine malignancies. Based on an average daily dose of 20 mg, the estimated worldwide patient exposure to Nolvadex (tamoxifen citrate), since its first market introduction, is more than 12 million patient years (information on file, AstraZeneca). AstraZeneca’s database contains worldwide literature reports of adverse events, serious adverse events from clinical trials, and all spontaneous postmarketing adverse event reports. From these, 942 uterine malignancies were identified, approximately 48% of them in the United States. Uterine cancer (including endometrial adenocarcinoma) was noted in 85% of the reports (802 reports) and uterine sarcoma in 15% (140 reports). All 140 reported cases of uterine sarcoma were further stratified according to histologic type. Seventy-three percent of these sarcomas were MMMT, approximately one third of which had a fatal outcome. In the NSABP data, nine of the 12 sarcomas found were MMMT or carcinosarcomas.

In a population-based series of 324 women diagnosed with endometrial cancer after breast cancer, identified by four SEER registries, the
proportion of women with sarcomas was similar among those who had taken tamoxifen (11 of 146, 7.5%) and those who had not (12 of 178, 6.7%).

Women with sarcomas had worse endometrial cancer–specific survival than did those with adenocarcinomas (P < .0001). However, the prognosis of women with uterine sarcomas or adenocarcinomas who had taken tamoxifen was not worse than that of women not exposed to tamoxifen; in fact, for both histologic subgroups, the probabilities of survival were greater among women treated with tamoxifen (median follow-up, 85 months).

This study, like the NSABP data and the report by Bergman et al., indicates that tamoxifen treatment is associated with an increased risk of both endometrial adenocarcinoma and uterine sarcoma. While the NSABP data suggest that the proportional increase in risk of sarcoma due to tamoxifen could be greater than that for adenocarcinoma, the SEER study data do not support that conjecture, nor is a biologic explanation for such a phenomenon readily apparent.

How should this information be incorporated into treatment decisions for women considering tamoxifen therapy? For women with hormone receptor–positive invasive breast cancer, tamoxifen has been demonstrated to improve relapse-free and overall survival. For women with ductal carcinoma-in-situ or for those who are at high risk for breast cancer for whom survival benefits have not yet been documented, the risks and benefits of tamoxifen therapy should be thoroughly assessed for each patient. Because patients with uterine sarcomas have been included in estimates of risk for endometrial cancer, the detailed risk–benefit statistics previously published can be used to determine which women may benefit from tamoxifen for reduction of breast cancer risk. Physicians should be aware that a small proportion of uterine malignancies that occur in women who take tamoxifen may represent uterine sarcomas. In deciding if tamoxifen therapy is warranted, all potential life-threatening adverse events associated with tamoxifen should be considered, including endometrial adenocarcinoma or uterine sarcoma, thromboembolic events, and stroke. When tamoxifen therapy is recommended, women at risk for endometrial cancer should undergo annual gynecologic examinations and should be counseled to seek prompt medical attention if they experience any gynecologic symptoms such as menstrual irregularities, vaginal bleeding, change in vaginal discharge, or pelvic pain or pressure.

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REFERENCES


Hypersensitivity Reaction (HSR) to Docetaxel After a Previous HSR to Paclitaxel

To the Editor: Hypersensitivity reactions (HSRs) to paclitaxel are well described in the oncology literature. The etiology of these reactions has been the source of much speculation, with Cremophor EL, the diluent for the insoluble paclitaxel, commonly blamed. Premedication with corticosteroids and H1 and H2 receptor antagonists successfully reduces the incidence and severity of the HSR. Retreatment strategies have been developed to allow continuation of the paclitaxel infusion after a HSR, and patients who experience a severe
reaction or a second HSR after reinitiation of therapy have received further cycles after undergoing a formal desensitization protocol.\textsuperscript{2,3} Successful substitution of paclitaxel with docetaxel, another taxane with similar efficacy, has also been described.\textsuperscript{6-8} However, docetaxel has also been implicated in causing acute HSR.\textsuperscript{3,4,9} and corticosteroid premedication is recommended. Cremophor EL is not the vehicle for docetaxel (dissolved in Tween 80), which suggests that the taxane moiety is a likely etiologic factor in the incidence of HSR seen with these medications.

In support of this hypothesis, we report a case of a patient who experienced HSR to both agents. A 56-year-old woman underwent surgical debulking at a nearby institution for a uterine mass. This was diagnosed as a poorly differentiated serous papillary adenocarcinoma of the endometrium with bilateral ovarian and peritoneal metastases, and she was prescribed combination chemotherapy with paclitaxel and carboplatin. Before commencement of the paclitaxel infusion, she received standard premedication with dexamethasone, promethazine, and ranitidine. After infusion of 19 mL of paclitaxel (300 mg diluted in 500 mL of dextrose 5% to be administered over 3 hours), the patient experienced sudden onset of dyspnea, wheeze, back pain, and facial flushing. This was followed by a loss of consciousness for approximately 60 seconds, during which time she desaturated as low as 81% (by pulse oximetry) on room air. The paclitaxel infusion was ceased and the patient responded to treatment for an acute HSR. After a period of observation, carboplatin was administered without incident.

After this episode, a decision was made to substitute docetaxel for paclitaxel, and the patient was transferred to our unit for continuation of chemotherapy 3 weeks later. The patient was given the recommended oral corticosteroid premedication, and 30 minutes before commencing the docetaxel, she received additional injections of dexamethasone and promethazine. Five minutes after initiation of the docetaxel infusion (132 mg diluted in 250 mL of sodium chloride 0.9% to be administered over 1 hour), the patient complained of dyspnea and hot flushes, became mildly cyanotic, and desaturated to 90% on room air. The infusion was immediately ceased and the patient was managed appropriately. Again, after a period of observation, carboplatin was administered without incident. She has since completed a third cycle of carboplatin monotherapy without sequelae.

To our knowledge, this case documents the first case of hypersensitivity to docetaxel after a previous HSR to paclitaxel and illustrates the continuing need for caution when administering the taxanes. It also supports the hypothesis that while the Cremophor EL diluent may indeed be responsible for many of the HSRs to paclitaxel, it is probable that there is a distinct subgroup of patients who are hypersensitive to the taxane component of these agents. To confirm this, we are endeavoring to determine whether antitaxane antibodies can be detected and if a suitable assay is available.

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REFERENCES

ERRATUM

In the June 1, 1999, issue of the Journal of Clinical Oncology, an article by Tang et al, entitled “Expression of BAG-1 in Invasive Breast Carcinomas” (J Clin Oncol 17:1710-1719, 1999) had an incorrect spelling of the second author’s last name. The correct spelling is Shehata, not Shaheta.