To the editor:

Treatment of children with acute myeloid leukemia

In a recent article, Woods et al report that postremission bone marrow transplantation (BMT) produced better overall survival than chemotherapy in children with acute myeloid leukemia (AML). They also indicate that intensive timing induction improved postremission survival. Their study is impressive in its design, conduct, and magnitude, but their article raises several questions.

First, in comparing initial characteristics of patients in the allogeneic BMT (allo-BMT) and chemotherapy groups, no mention is made of ethnicity or socioeconomic and insurance status. Because these appear to be important variables in accessibility to allo-BMT and may also influence prognosis, should they not be taken into consideration? Is it possible that access to allo-BMT itself is a selective factor for better prognosis?

Second, the article compares overall survival after remission rather than from diagnosis. As described elsewhere, the remission induction mortality due to drug toxicity was 12% for the intensive timing group and 5% for the standard group. Is it possible that this higher treatment-related mortality during induction removed from the intensive-timing group patients with less favorable prognosis, for example, patients more vulnerable to chemotherapy toxicity and interruption during postremission chemotherapy? In other words, were the postremission intensive-timing patients selected for better prognosis by the mortality of the intensive-timing induction?

Third, as the article points out, survival curves for AML do not plateau until 6 or more years. Because the plateau is the closest measure of cure or near-cure, the plateaus must be compared to determine curability. Comparison of the 6- and 7-year survivals of the allo-BMT and chemotherapy groups in Woods et al’s Figure 2 reveals no apparent significant difference. This is reflected in the configuration of the 2 survival curves, which indicate that the wide gap at 3 years progressively narrows in subsequent years. In children, should entire survival curves or plateaus be used to compare success? To revive an argument from the 1960s, is the prime goal of treatment to prolong survival or to cure leukemia?

Finally, the article justifiably celebrates progress in curing children of AML. But for the sake of perspective, should not event-free survival and overall survival from diagnosis be indicated, and should not the treatment-related mortality and morbidity, late and early, be summarized?

From my reading of this article and similar reports cited by Woods et al, I fail to reach their conclusion that allogeneic BMT is the treatment of choice for children with AML in first remission who have a matched related donor.

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References


Response:

A comparison of allogeneic bone marrow transplantation (BMT), autologous BMT, and chemotherapy in pediatric acute myeloid leukemia

We thank Drs Creutzig et al, Drs Horan and Korones, and Dr Pinkel for their comments regarding our recently published study. We would like to respond to several points that were raised.

As Creutzig et al point out, we and others have documented that in every large, published, randomized trial of postremission therapy in children with acute myeloid leukemia (AML) in first remission, superior results, often significant, have been found in the allogeneic bone marrow transplantation (BMT) arm, including our study. Several of these studies used advanced intensive treatment strategies, both in induction and in the chemotherapy postremission phase. Even the Medical Research Council (MRC) trial,3 which Creutzig et al cite, shows a superiority in survival for allogeneic BMT (70% versus 60%, at 7 years; P = .10). Although no one has published a formal meta-analysis, results would clearly favor allogeneic BMT. Compliance with the allogeneic BMT arm was 94% in our study,4 precluding ethnic, socioeconomic, or insurance status bias.

Creutzig et al raise the interesting question of whether patients with favorable cytogenetics or other good prognostic factors might not need allogeneic BMT. Although beyond the scope of the overall paper, in Children’s Cancer Group trial (CCG)-2891 we could not show the value of favorable cytogenetics, based on adult trials, in determining postremission therapy. For example, in patients with 16q abnormalities, 77% receiving allogeneic BMT are alive at 6 years, compared with 56% receiving aggressive postremission chemotherapy (P = .39). Even in our large trial, the number of affected patients with specific cytogenetic abnormalities is too small to make definitive conclusions. We certainly agree that patients with acute promyelocytic leukemia and t(15;17) should first be treated with all-trans-retinoic acid (ATRA)–containing regimens. As noted in our original CCG-2891 manuscript, since 1992 CCG patients with acute promyelocytic leukemia have been enrolled in ATRA-containing protocols not offering BMT, and this practice continues. We furthermore advocate allogeneic BMT only when a matched family donor is available, in children without Down syndrome.

Our study emphasizes the importance of long-term follow-up with survival as the ultimate, most important endpoint. All 3 of our postremission arms showed plateaus after 4 years in patients receiving intensively timed induction therapy.1(Fig1) This is in contrast to the ongoing drop-off in survival in patients receiving standard timing.1,10(Fig2) Late-transplant deaths were seen in standard-timing patients, both because of ongoing relapses and from chronic graft-versus-host disease. This phenomenon has been well described: although the initial, pioneering reports from the Fred Hutchinson Cancer Research Center suggested survival in AML patients undergoing allogeneic BMT of almost 65%,2 long-term studies revealed outcomes closer to 45%,6 during an era when less aggressive induction therapy was utilized. We agree with Horan and Korones that no one has done a study critically examining matched-related-donor (MRD) BMTs utilized in relapse. But results of matched-unrelated-donor BMTs in second or subsequent remission may be as efficacious as MRD BMT.7 To summarize, the largest trial to date, which had an extremely high completion rate and utilized aggressive induction and postremission chemotherapy, indicates that allogeneic BMT remains the treatment of choice for the vast majority of children with AML in first remission. “Cure,” not prolonging survival, is the end-point.

With respect to overall survival, 49% from diagnosis for the 539 patients receiving intensive-timing induction, results would have been a bit higher had we not randomized 177 patients to autologous BMT. It is highly unlikely that intensive timing “selects” for patients more vulnerable to chemotherapy: the difference in induction deaths between intensive and standard timing, 9% (12% versus 3%, respectively), is much less than the difference in survival after achieving remission, 17% (61% versus 44%).

The Berlin-Frankfurt-Münster (BFM) studies cited by Creutzig et al do not represent a comparable patient population to our study, primarily performed in North America. CCG trials accept patients up to the age of 21 and include a much more heterogeneous population than in either the German8,9 or British3 studies. Only 67% of our patients are of northern European descent, with 25% of patients either African American or Hispanic, 3% Asian, and 5% “other.” In the past 2 CCG trials, including CCG-2891, African Americans and Hispanics have done significantly worse (36% survival at 6 years, both induction arms, versus 47% for whites; P < .001). Specific results will be published in a future manuscript. It is well known that there are striking differences in the incidence of AML subtypes among various geographic locations.10 There are also major genetic differences that determine outcome to therapy.11 It is most difficult to compare outcome of patients in various geographic areas when one is not controlling for important variables, including genetic differences.

We agree with Creutzig et al that “allogeneic BMT [in fact, all treatment] should always be considered in context with the applied protocol.” Although the BFM Group has reported excellent results in children receiving AML therapy, the routine use of cranial radiation to achieve these results12 is questionable. The late, deleterious effects of cancer and its treatment cannot be overestimated in children. We have seen a dramatic decline in the short-term and long-term morbidity and mortality associated with allogeneic BMT. We also use conditioning regimens that do not include total body irradiation, hence sparing the brain exposure to an agent that is well known to affect long-term development.13

Future North America–wide Children’s Oncology Group trials in childhood AML will continue to utilize allogeneic BMT in first remission for patients with matched family donors, while continuing to look for favorable subtypes that may do well with less aggressive therapy.

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References

To the editor:

Screening for c-mpl mutations in patients with congenital amegakaryocytic thrombocytopenia identifies a polymorphism

Congenital amegakaryocytic thrombocytopenia (CAMT) is an uncommon disorder, characterized by an isolated thrombocytopenia and the almost complete absence of megakaryocytes in the bone marrow. Several studies have indicated that the origin of CAMT is an intrinsic stem cell defect.1-3 Recently, we and others have demonstrated the presence of mutations in the thrombopoietin-receptor gene, c-mpl, as a possible cause of CAMT.4,7 Although some mutations directly predict loss of Mpl function, it has not been established that others, notably those that lead to an amino acid substitution, also directly predict this loss.

To exclude that the mutations we found in our patients represent non–disease-related polymorphisms, we screened 50 healthy donors (100 alleles) for the presence of the different mutations by either sequence analysis or allele-specific restriction analysis.4 None of the healthy donors were carriers of our reported CAMT-associated mutations. In one new CAMT patient, 3 heterozygous mutations were observed: a G-to-C substitution at nucleotide 305 in exon 3, predicting an arginine-to-proline substitution at codon 102; a G-to-A transition at position 340, also in exon 3, leading to a valine-to-methionine replacement at codon 114 (Mpl-114V/M); and a G-to-C substitution in the fifth nucleotide of intron 3, which leads to loss of the splice site 3’ of exon 3. Screening of 50 healthy donors revealed that 4 were heterozygous carriers of the G340A mutation. The other mutations were not observed in this population. The c-mpl-340A gene thus seems to have a frequency of 0.04 in a white Dutch population. Functional studies should reveal whether this Mpl-114V/M polymorphism influences the function of Mpl.

Recently, Ballmaier et al12 reported c-mpl mutations in another series of patients with CAMT. One of their patients was a homozygous carrier for 2 different point mutations. One mutation predicted a stopcodon in exon 3. The second mutation was the G340A mutation, which we also found in healthy donors. Therefore, we propose that the first mutation plays a role in the development of CAMT in this patient. The G340A may not be involved in CAMT, and its presence in 2 CAMT patients may be incidental.

In conclusion, mutations that predict amino-acid substitutions found by genetic screening of patients with CAMT can be due to polymorphisms of the c-mpl gene. The relation of such mutations to disease should be proven by functional studies with the mutated protein.

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References

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