CURE IN ACUTE PROMYELOCYTIC LEUKEMIA: NOW MORE READILY ACHIEVABLE WITH LESS TOXIC THERAPY

To the Editor:

Previous reports dating to the 1970s have indicated that cure may be more common in acute promyelocytic leukemia (APL) than in virtually all of the other subtypes of acute myelogenous leukemia (AML). Recent studies have suggested that perhaps other AML subtypes may also do well. Patients with M2 and t(8;21) and M4 with inv16 can expect a good outcome, but long-term survival remains more widespread in patients with APL and t(15;17).8-10 This result has followed traditional treatment but can potentially be improved further with delivery of more effective induction therapy.

With an anthracycline-, anthraquinone-, or amsacrine-containing induction regimen as many as one third of the previously untreated patients can be expected to achieve long-term survival.

Recent results with all-trans retinoic acid (tRA)13-15 have raised
the possibility that an alternative to traditional chemotherapy exists for induction of remission and that chemotherapy, after tRA-induced remissions, may potentially offer a better outcome. However, it is important to recognize that chemotherapy administered after induction of remission with tRA will not be curative in all patients and may add considerable toxicity. The question that we now face is whether it is necessary to find better agents for the postinduction period, or whether simply changing the sequence can offer cure to an increased number of patients.

Early on, intracerebral hemorrhage was identified as a common, fatal complication of induction chemotherapy in patients with APL. However, our recent study has shown that intravenous (IV) administration of 2 U of fresh frozen plasma (FFP) and transfusion of 6 U of platelets every 12 hours accompanied simultaneously by IV heparin can eliminate this risk entirely, even during intense chemotherapy. In our series of more than 60 patients with APL, hemorrhage occurred in a solitary patient in whom adequate platelet transfusions were not available on the fourth day of treatment. Therefore, this ability to prevent bleeding entirely during induction chemotherapy removes "prevention of hemorrhage during chemotherapy" as a strong argument supporting the use of tRA over chemotherapy for induction of remission. The question that we now face is whether delivery first of (1) traditional doses of commonly used drugs, (2) more effective chemotherapy, or (3) tRA first represents the most appropriate start toward curative treatment.

Historically, there was never a strong argument that favored one induction regimen over another, although the use of daunorubicin was always important. A modest increase in the daunorubicin dose by 25% or increasing the cytarabine infusion by 3 days (from 7 to 10 days) could hardly be expected to dramatically increase leukemia cell kill or to affect the cure rate. More recent experience with high-dose/short-course mitoxantrone with high-dose cytarabine suggests that a significant increase in the "quality" of remission may be possible (see below) and that tRA, while not curative in all patients at the time of diagnosis, may yet be curative when administered at a time of minimal residual disease. How low the leukemia burden must be for tRA to be curative remains to be clarified.

Since the initial report on the effectiveness of daunorubicin, the cure rate has remained fixed at approximately 30%. One wonders whether induction of remission of "better quality" by chemotherapy alone could lead to a significantly lower relapse rate and whether tRA treatment after complete remissions of "better quality" could lead to a higher cure rate.

In our recent experience in previously untreated patients with APL, intense chemotherapy has induced remission in 16 of 18 patients and, in the 5 patients receiving the most intense therapy, there has been no relapse in the last 2 years (in these patients, induction consisted of cytarabine 3 g/m² over 3 hours once a day × 5 doses with mitoxantrone 80 mg/m² × 1). If these results continue, they support the thesis that the "quality of remission" is related to the quality of the drug and, with many drugs, to the quantity of the dose that is administered. Daunorubicin 45 mg/m² × 3 with cytarabine 100 mg/m² × 7 does not cure everyone, but it may induce remission of adequate quality for cure in some patients with subsequent tRA. However, because traditional "induction" doses require that one third of the patients receive a second course to achieve their remissions, it is unlikely that this will remain the treatment of choice. Cure may be possible in the most sensitive patients in first remission receiving postremission tRA, but tRA administered in subsequent remissions may not be curative. Perhaps it is the quality of remissions that follows induction therapy that determines if tRA will be curative. Thus, it remains possible that even optimal induction chemotherapy followed by tRA may not prevent relapse in every patient.

If necessary, we should be prepared to increase the dose of induction chemotherapy, always monitoring the cost of treatment. Worsening of liver function, stomatitis, cardiac toxicity, or prolonged cytopenia will set a limit on the dose of induction therapy. At the current high doses of mitoxantrone and cytarabine, the risks have been small and we have been able to add etoposide up to a dose of 150 mg/m² × 3 without significant toxicity. On the other hand, if cure becomes universal, we should consider the possibility that chemotherapy doses, lower than what we currently offer, may be sufficient when combined with tRA.

Recent publications have raised the possibility that tRA administered first might be favored because the toxicity of this induction therapy may be less than experienced with traditional chemotherapy. While this may have been true in an earlier era, the recent methods used to prevent bleeding are now completely effective and that argument does not hold. If we compare the dose of chemotherapy that has been used in the post-tRA-induced remissions with the chemotherapy dose that we now administer at the time of diagnosis (mitoxantrone/high-dose cytarabine, mitoxantrone/high-dose cytarabine/etoposide), it is clear that "near curative" chemotherapy is best given at the time of diagnosis, not in consolidation. Delivery of the highest dose can only be administered at a time when hematopoietic stem cells are resting, and not when these cells are rapidly proliferating, as at the time of complete remission.

This experience suggests that, in the future, bone marrow transplantation may no longer be a therapeutic option in patients with APL in first remission. Induction of a "quality" remission followed by tRA may be even more effective than induction of remission followed by bone marrow transplantation (BMT). BMT in the future will probably have to be limited to patients in "early" relapse or may best be administered at the time of second complete remission. The next few years will hopefully show that cure may not only follow one course of intensive chemotherapy followed by tRA, but that it may also be possible after treatment regimens that are less intense and less toxic.

The incidence of relapse after second or third remission has been almost universal, but tRA offered in the setting of a higher quality remission may still offer a solution without BMT to this group of patients. It is also possible that a more effective differentiating agent may yet find a role.

ZALMEN A. ARLIN
TAUSEEF AHMED
Department of Medicine
Division of Neoplastic Diseases
New York Medical College
Valhalla

REFERENCES

Cure in acute promyelocytic leukemia: now more readily achievable with less toxic therapy [letter]

ZA Arlin and T Ahmed