Commentary (Dutcher/Wiernik): Current Management of Acute Lymphoblastic Leukemia in Adults

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Acute lymphoblastic leukemia (ALL) in adults is clearly a "different disease" than ALL in children—a fact that is well documented in the article by Ong and Larson. As they indicate, more than half of adult patients relapse despite modern therapy, most within the first 2 years. It should be pointed out, however, as is mentioned at the beginning of the article, that "modern" induction was defined by Cancer and Leukemia Group B study 7612—a study begun in 1976 [1]. Thus, induction therapy has not changed substantially in 20 years. The addition of consolidation therapy and prolonged maintenance therapy has resulted in modest increases in response duration, but despite many variations on current regimens, there has been little change in outcome during the past decade.

Recent progress in the treatment of adult ALL has related primarily to a better definition of subgroups with differing prognoses, based on immunophenotype and cytogenetics. By separating patients into prognostic groups, certain treatment approaches may appear better, but in fact, taking the entire group of adult patients, few recent therapeutic advances can be documented. The same truths that hold for childhood ALL also apply to adult ALL:
1) There are clinically defined prognostic groups.
2) There are molecularly defined prognostic groups characterized by cytogenetic abnormalities.
3) Seemingly better treatment, ie, more aggressive therapy, has its major impact on the patients with better prognosis, who constitute the smallest subgroup.

Why the Limited Progress?
The major reason for this limited progress is the absence of new drugs with enhanced activity against ALL. Unlike acute myeloid leukemia (AML), in which a small incremental improvement appears to have been made through the addition of etoposide (VePesid) to standard induction therapy; the development of new, better anthracyclines, such as idarubicin (Idamycin); and the dramatic effect of an entirely new agent, all-trans retinoic acid, no such agents have appeared on the scene for ALL. In addition, even with the application of high-dose therapy and both allogeneic and autologous bone marrow transplantation to both AML and ALL, it appears that AML may respond better to dose intensification than does ALL [2,3]. Thus, it is imperative that any new agents with antileukemic activity be explored in ALL, or we will spend the next decades utilizing variations on the theme of the current decade.

Non-Anthracycline-Containing Regimen
Of interest, and despite the results of CALGB 7612 showing the benefit of daunorubicin (Cerubidine), we have published and updated the results of a non-anthracycline-containing regimen that demonstrates a response rate and response duration equivalent to more "modern" studies. This regimen, MOAD, is based on the pharmacologic interactions among methotrexate, Oncovin, and asparaginase (Elspar) [4]. The corticosteroid used is dexamethasone rather than prednisone, as the former agent has greater central nervous system (CNS) penetration.

During the induction phase, asparaginase is given 24 hours after methotrexate to function as both an antileukemic agent and as a rescue for normal cells from methotrexate toxicity. Methotrexate dose is escalated during each induction and consolidation cycle to combat induced drug resistance, and asparaginase is used as the rescue throughout these courses. In the cytoreductive phase,
vincristine is administered 24 hours before methotrexate, which promotes methotrexate influx into tumor cells and thereby possibly lessens drug resistance. Methotrexate is given at a very high dose during cytoreduction, in 12 monthly cycles with leucovorin, and serves as both systemic therapy and CNS prophylaxis. Subsequent monthly maintenance therapy consisting of vincristine, dexamethasone, methotrexate, and mercapto- purine (Purinethol) is continued for a total of 3 years. For patients treated with MOAD who have prognostic factors comparable to those in the Linker, Hoelzer, Hussein, Radford, and Kantarjian studies referred to by Ong and Larson, the remission rate is identical (80%), and the median complete remission duration of 27+ months and 3-year disease-free survival rate of 42% are also comparable. The intensive use of methotrexate in this regimen and/or the attention paid to pharmacologic interactions may account for the comparable results. The MOAD regimen is also highly active in relapsed patients and some long-term survivors without the addition of bone marrow transplantation.

**New Anti-ALL Drugs Badly Needed**

Overall, however, we are still in a very difficult situation with adult ALL, in which we continue to manipulate our current armamentarium and to draw analogies from the treatment of AML in an attempt to gain small increments.

What we badly need are new agents with anti-ALL activity. We should also keep in mind that most advances are most notable in the better-prognosis patients, and these patients, too, must be included in clinical trials of new therapies. Now that we have realized the potential and limits of bone marrow transplantation, we should renew our efforts to find new drugs. Until potential new agents appear on the scene, unfortunately, we shall continue to be frustrated by our therapeutic limits, despite a better understanding of the molecular changes in ALL. Perhaps new biologic therapies will offer novel therapeutic directions, but we await studies confirming their potential.

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