

ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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Pediatric Regimens for Adult Acute Lymphoblastic Leukemia

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H&O How are adult patients with acute lymphoblastic leukemia (ALL) being treated today, and how is it different from pediatric regimens?

WS Most adult ALL regimens are based on pediatric regimens that have been adapted over the years. For the most part, adult regimens are quite similar to what is used in pediatrics. The main difference is that adult regimens have focused on the intensification of certain drugs, whereas the pediatric regimens have tinkered with the intensification of the dose schedule.

There are many drugs that are active in ALL. In general, adult cooperative group studies have focused on dose intensification of agents that are myelosuppressive (eg, cyclophosphamide, cytarabine [Ara-C], and daunorubicin). In addition, some of the adult trials have been exploring stem cell transplant in first remission—the potential for introducing a new immune system to induce a “graft versus leukemia” effect. On the other hand, the pediatric cooperative groups have been fine-tuning their regimens, focusing on a different set of active agents for ALL, including the glucocorticoids (prednisone or dexamethasone), vincristine, and asparaginase in particular.

H&O What is the reasoning behind this difference in approach and treatment outcome?

WS One of the reasons pointed out is that the biology of the disease in pediatric and adult patients are different. There are certain recurring chromosomes, cytogenetic abnormalities, and recurring molecular abnormalities

that are prevalent in childhood ALL but not prevalent in adult ALL. These abnormalities render quite impressive sensitivity to chemotherapy regimens and most likely contribute to the high cure rate that is seen in pediatric ALL when compared to ALL in adults. In contrast, the adult patients tend to have cytogenetic abnormalities that render more resistance to the current regimens.

For example, one of the most common abnormalities in children ages 2–10 is a cryptic translocation, the t(12;21), which results in a fusion gene, TEL-AML1. This fusion gene is associated with an extraordinarily good prognosis and is present in up to 30% of precursor-B ALL in children ages 2–10. These children have an extremely high remission rate and a disease-free survival that approximates 90%. In contrast, the TEL-AML1 fusion gene is hardly ever seen in patients over the age of 15; we do not know why that is.

The other cytogenetic abnormality that occurs frequently in the best risk group (children ages 2–10) is hyperdiploid cytogenetics, where many of the chromosomes are duplicated. Hyperdiploidy is also associated with an extraordinarily good prognosis in pediatric ALL. However, hyperdiploid ALL occurs much less frequently in people over the age of 15; there are too few patients who are over 15 and have hyperdiploid ALL to make a good statement about whether it has the same good prognosis in adults with hyperdiploid ALL.

On the other hand, the Philadelphia (Ph) chromosome, which has been associated with a very poor outcome in ALL (ie, survival rates of approximately 9 months until the recent introduction of tyrosine kinase inhibitors [TKIs]), dominates in adult ALL. The Ph chromosome only occurs in about 5% of children,

but is seen in up to 50% of adults over the age of 60 with precursor-B cell ALL. Although these patients are now being treated much more successfully with combinations of chemotherapy and TKIs such as imatinib (Gleevec, Novartis) or the next generation TKIs that target the *BCR-ABL* tyrosine kinase, it highlights how the different biology in children and adults leads to different treatment approaches and treatment outcomes.

H&O How are these regimens effective in younger adults?

WS About 8 years ago, with the Cancer and Leukemia Group B (CALGB) and the Children's Cancer Group (CCG), I compared pediatric and adult ALL treatment outcomes in young adults (ages 16–20).¹ Because there is an overlap in this particular age group in the sense that they are in the care of either pediatricians or medical oncologists, and regimens for each were similar, the hypothesis was that patients would do about the same, given the fact that they would have the same biology of disease. However, the outcome differences were striking. The 16–20 year-olds who were treated on adult group protocols did much worse (event-free survival [EFS], 34%; overall survival [OS] at 7 years, 46%) than those who were treated with the children's oncology group protocol (EFS, 63%; OS at 7 years, 67%; $P < .001$).

Many reasons could have contributed to this difference: The pediatric regimen included intensified vincristine, asparaginase, and the prednisone/dexamethasone—the glucocorticoids, whereas the adult protocols included intensified the daunorubicin, Ara-C, and cyclophosphamide. Also, the pediatric regimens included more frequent and earlier introduction of prophylactic treatment to the central nervous system via intrathecal therapy, and mandated longer maintenance therapy than the CALGB regimen.

Additionally, we speculated that other reasons—patient behavior, adherence to medication, availability to receive treatment with insurance coverage, financial and emotional support, socioeconomic status—could have also contributed to the difference in results. It was presumed that pediatricians are more familiar with ALL because it is the most common form of leukemia that they treat. Moreover, they have the cooperation and aid from parents; because much of ALL treatment relies on self-administered oral medications, parental oversight becomes very significant. In contrast, ALL is a rare disease for medical oncologists, and it is possible that they were less rigorous in adhering to the strict treatment schedules required.

Therefore, in order to further investigate the many unanswered questions raised by this study we are currently treating that group of young adult patients and

extending the inclusion criteria to age 30, using a regimen identical to what the pediatricians have successfully used. We are curious to see if the treatment alone is better, whether adult oncologists adhere to the treatment as well as the pediatricians. We will also obtain, through questionnaires, information about the demographics of the patients who are treated on the adult protocol (eg, psychosocial and socioeconomic status). We are currently gathering this information in a prospective fashion, and the trial is ongoing. It is led by CALGB (Intergroup trial C10403) in joint effort with the Southwest Oncology Group and the Eastern Cooperative Oncology Group (ECOG). We are hoping to accrue 5–6 patients a month; we currently have approximately 45 patients enrolled. It will take a few years to fully accrue to this study and then begin to evaluate treatment feasibility and efficacy.

H&O Are there any other studies that are looking into this?

WS Many international research groups have also begun to investigate this area. Interestingly, other international pediatric and adult cooperative groups have compared their outcome results of adolescents and young adults with ALL and have found exactly the same outcome differences: the pediatric regimens had better outcomes than the adult cooperative group trials.

Dr. Dan DeAngelo and his colleagues at the Dana-Farber Cancer Institute investigated whether an intensive pediatric regimen could be administered to adults with ALL (age range, 18–50 years);² induction chemotherapy included doxorubicin, prednisone, vincristine, high-dose methotrexate, L-asparaginase, and triple intrathecal therapy. The study found that the administration of a dose intensified pediatric regimen to adults with ALL is feasible.

Dr. Josep-Maria Ribera's ALL-96 study from Spain compared the toxicity and results of a pediatric-based protocol in adolescents aged 15–18 years and young adults aged 19–30 years with standard-risk ALL.³ They found that the response to the pediatric protocol was identical in adolescents and young adults, justifying the use of pediatric regimens for ALL patients who are over the pediatric age range.

Most recently, the GRAAL-2003 study, led by France's Dr. Francoise Huguet, tested a pediatric-inspired treatment that included intensified nonmyelotoxic drugs (eg, prednisone, vincristine, L-asparaginase) in adult patients with ALL up to 60 years;⁴ the study found that the regimen markedly improved the outcome of adult patients at least until the age of 45 years.

Although there are many studies that are investigating the efficacy and safety of these pediatric ALL

regimens in older patients, my opinion is that there are some concerns with trying to get intensified asparaginase, vincristine, and glucocorticoids into adults over the age of 30. This is because, for reasons that have not been completely characterized, older adults do not tolerate these agents as well as children do, and more toxicities are reported in the adult population. Older patients may have a harder time metabolizing those drugs and it is likely that there will be a higher toxicity associated.

However, if the data in younger adults are correct—and it is still a big “if” in my mind—the EFS for these pediatric ALL regimens is significantly better than what we have reported on any of our contemporary adult trials. Encouraging survival has also been reported by the ECOG and Medical Research Council in Great Britain for a selected group of younger adults (< 35 years old) who received an allogeneic stem cell transplant in first remission. In their study, OS for patients with a matched sibling donor was 53%.⁵

In summary, while I am very encouraged about the improvements in outcome for young adults with these regimens, I believe that the future holds even greater promise for progress if we can begin to successfully target pathways involved in disease pathogenesis. Targeting *BCR-ABL* with TKIs in Ph+ ALL, as we discussed

earlier, is the most successful example of this promising approach to date. Using a more refined treatment approach, the hope is to more effectively eradicate the leukemia stem cell to improve outcome and, hopefully, minimize treatment toxicity by “molecular tailoring” of the therapeutic approach.

References

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