What Pediatrics Can Teach Us

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By Frederick R. Appelbaum, MD [1]

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The cure of childhood acute lymphocytic leukemia (ALL) stands at the top of medicine's achievements in the struggle against cancer. Those of us who treat adults with ALL are disappointed that we haven't been able to keep pace. A reasonable hypothesis is that increased focus on the reasons for these age-related differences should give us clues about how to improve outcomes for adults with ALL.

<table>
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<th>TABLE</th>
<th>Comparative Outcomes of Adolescent and Young Adult ALL Patients Enrolled in Pediatric vs Adult Trials</th>
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As acknowledged in the excellent review by Rabin and Poplack,[1] we don't really understand all of the reasons for the discrepancies between outcomes in children and outcomes in adults; however, one fascinating and disturbing observation has emerged from studies comparing outcomes in adolescent and young adult (AYA) patients with ALL enrolled in pediatric clinical trials with the outcomes of those enrolled in adult clinical trials. As outlined in the Table, despite similarities in age and observable disease characteristics, survival is generally better for AYA patients enrolled in pediatric trials, in some cases remarkably so.[2-8] There is no simple explanation for these differences, but as discussed by Stock,[9] Schiffer,[10] and others, variations in protocols, in physicians' approaches to treatment, or in the patients themselves may contribute. In general, pediatric protocols tend to use higher cumulative doses of glucocorticoids, vincristine, and L-asparaginase, whereas adult regimens rely more on anthracyclines and alkylators. Treatment of ALL is a large component of a pediatric oncologist's practice, whereas ALL is a relatively uncommon disease for most adult oncologists. Perhaps pediatricians are therefore more comfortable with the disturbing but ultimately reversible toxicities associated with ALL therapy and thus more reluctant to alter schedules or reduce doses. Finally, it seems highly probable that AYA patients who are seen by adult oncologists are more likely to be living independently than those seen by pediatricians, and thus face more challenges in protocol compliance. A nineteen-year-old with ALL seen by a pediatrician will likely be brought by a parent, whereas a nineteen-year-old with ALL seen by an adult oncologist may already be a parent.

While any and all of these hypotheses are possible, we may soon have at least a partial answer. Cancer and Leukemia Group B and the Southwest Oncology Group are currently conducting a trial in adolescents and young adults with ALL (C10403) using the exact regimen that is being concurrently studied by the Children's Oncology Group. Careful documentation of socio-economic status and protocol compliance are parts of this study. When completed, we will be able to directly compare outcomes of AYA patients treated using exactly the same protocol at pediatric vs adult centers, as well as compare the socio-economic status and protocol compliance of patients, thus unraveling some of the mystery surrounding the findings in the Table. While protocol, practice, or compliance may explain some of the differences between childhood and adult ALL, there are, without question, age-related changes in the distribution of disease subtypes that impact outcome. ALL in adults is more often associated with t(9;22) translocation, and is more
often of mature T- or B-cell phenotype. Thankfully, we now have therapeutic agents that can target each of these subsets, including tyrosine kinase inhibitors for t(9;22) ALL, nelarabine (Arranon) for T-cell ALL, and rituximab (Rituxan) for mature B-cell ALL. There are also age-related changes in the ability of patients to tolerate certain chemotherapies. In particular, older patients more often have difficulty with vincristine-associated neuropathies and with asparaginase-associated pancreatitis and embolic phenomena. Here again, agents exist that may be able to ameliorate some of these problems, including liposomal vincristine. But even among apparently similar subtypes of ALL, the disease appears to be inherently more sensitive to treatment in children than in adults. The underlying reasons for this difference are not known, but there are a number of new agents that offer reason for optimism in the treatment of ALL, including antibodies against CD19, CD22, and CD52, bi-specific antibodies, anti-CD22 immunotoxins, and chimeric antibody receptor T cells, among others. However, no randomized trials have been completed in the United States to test the utility of tyrosine kinase inhibitors, nelarabine, rituximab, liposomal vincristine, or any other of the above-mentioned agents in adult ALL. And this may be the biggest and most important difference between childhood and adult ALL. Given the public interest in and moral imperative of a sick child, the majority of children with ALL are treated in clinical trials, and this, over decades, has gradually improved treatment outcomes. In contrast, our current fee-for-service care delivery system, coupled with an underfunded adult clinical trials program, has prevented the efficient conduct of clinical trials for uncommon diseases, such as adult ALL. Hopefully, we will continue to learn by mimicking what happens in childhood ALL and by paying attention to the advances made by our colleagues in other countries.

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References:
REFERENCES


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