

Will the Pediatric Regimen Work for Adolescents With ALL?

By Andrea Carter

Acute lymphoblastic leukemia (ALL) in children is often cited as an oncology success story, with a 5-year survival rate of 80% or more. Adolescents, however, haven't fared as well; for those aged between 16 and 21 years, the 5-year survival rate is 40%–60%.

At least part of the reason may be treatment differences, experts say. Many adolescents go to medical oncologists rather than pediatric oncologists and therefore receive the standard adult chemotherapy regimen. But studies suggest that the pediatric regimen, which is more intense and complex, could produce better outcomes in adolescents and young adults. Three of the large U.S. cooperative clinical trial groups are now conducting a large, multicenter, phase II trial to test whether the more intense regimen should be the standard treatment for adolescents and young adults, as well as children. The trial is enrolling patients aged 15–39.

But some physicians caution that the issue may not be as simple as one regimen versus another. Issues and barriers unique to caring for this age group can complicate treatments and

outcome. “I think it’s not just the treatment,” said Wendy Stock, M.D., of the University of Chicago, one of the trial’s principal investigators. “There is more to it, [such as] the psychosocial, physical, support staff, and biology.” The trial is also looking at some of these issues.

Accrual to the trial, CALGB-1043, which opened 4 years ago, remains steady, Stock said. As of June 2010, the trial had enrolled 112 patients; the accrual goal is 300. But 95% or more of centers treating adult patients have not yet opened the trial, according to adolescent and young-adult oncologist Archie Bleyer, M.D.

The small number of participating centers may reflect the psychosocial and clinical hurdles to treating this group.

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“In the entire life span, there are more challenges to one’s development in the adolescent years when a young adult is becoming who they want to be,” said Bleyer, now at the Oregon Health

and Science University in Portland. “Adding cancer on top of that explains why it is difficult to deliver treatment to this population.”

Young Children Do Better

ALL is primarily a young person’s disease. According to the National Cancer Institute, approximately 60.7% of patients with ALL are younger than 20 years at diagnosis. The high survival rates in children can drop to as low as 35% as patients approach 30 years.

Some of the reasons younger patients do better may have to do with biology. For instance, patients with hyperdiploidy and the TEL-AML1 fusion gene have a better survival rate, and these markers occur in about 25% and 20% of children, respectively, versus 5% and 2% of adults.

“If you sum all these up, the biology of ALL is very different, favoring a pediatric ALL,” said medical oncologist Hagop



James Nachman, M.D.

Kantarjian, M.D., at the M. D. Anderson Cancer Center in Houston.

Pediatric patients have also benefited from a long history of clinical trials for ALL. In a span of 50 years, 70–80 clinical trials have fine-tuned the pediatric protocol. The adult ALL treatment has not had nearly as many trials, according to Bleyer.

Younger patients have also benefited from management by pediatric oncologists who specialize in the disease. “For adult oncologists, an ALL patient is a relatively rare experience, and they are always on a learning curve, while we deal with it all the time,” said pediatric oncologist Ching-Hon Pui, M.D., at St. Jude’s Children’s Research Hospital in Memphis.

A 2008 study reported in the journal *Blood* suggested that whether a pediatric or adult oncologist treated an adolescent could determine the outcome. Stock and pediatric oncologist James Nachman, M.D., at the University of Chicago, compared the outcomes of adolescents in trials of the Children’s Cancer Group and CALGB, an adult cooperative trial group, from 1988 to 2001. At 7 years, the adolescents in the pediatric group had an event-free survival rate of 63%, compared with 34% for the CALGB adolescents, who had received the adult protocol.

“The results were surprising,” said Stock. “We didn’t expect them, and we were disappointed that we didn’t do as well as . . . the pediatric protocols.”

In general the pediatric regimen is more intense. In 1998 Nachman reported that children aged 1–9 years who responded poorly to the first phase of therapy had better outcomes with later, more intense phases. In a 2009 report in the *Journal of Clinical Oncology*, Nachman showed that a more intense regimen could also benefit adolescents who responded well to the initial therapy.

Nita Seibel, M.D., at the National Cancer Institute, said that the pediatric regimen gives about twice the amount of the steroids vincristine and L-asparaginase. Also, the chemotherapy introduced into the spinal fluid is nearly two times more than adults receive, she said.

Physicians have thought that older patients could not tolerate a stronger therapy. “There was initial talk that adults couldn’t take an increase in asparaginase,” said Nachman. “But it is certainly doable, and most adults have tolerated it well.”

Not So Simple

But even the staunchest advocates of the pediatric regimen for adolescents recognize the psychosocial and clinical issues that complicate treatment for this age group.

One problem is the complexity of the pediatric protocol. The pediatric treatment has five phases,

compared with one or two for the adult protocol. “The complexity is a huge obstacle,” said Bleyer. “It scares nurses, physicians, patients, and clinical assistants.” On its website, CALGB has posted a PowerPoint guide that a pediatric nurse developed to help new staff navigate through the trial.

Also, Seibel said, pediatric oncologists give the medicine at strict time points. Adult medical oncologists tend to be less rigid in keeping a schedule. The trial is looking at how well medical oncologists can follow the pediatric regimen’s schedule.

Another challenge in treating adolescents is patient compliance. Psychologist Lisa Schwartz, Ph.D., at the Children’s Hospital of Philadelphia, notes that most adolescents are forming goals about school, career, romantic relationships, and developing autonomy from parents. Health is not a priority.

Some pediatric centers offer support to help adolescents reconcile their treatment with their other goals. For example, at the Children’s Hospital of Philadelphia, physicians, nurses, and research staff are attuned to the challenges of this age of development. The hospital schedules teachers to assist patients with their schoolwork, and child life specialists plan group outings and a hospital prom to bring a feeling of normalcy during treatment.

Doctors also suspect that adolescents in pediatric centers have more family support, which helps them stick with the treatment. Parents are on hand to ensure that their children make their appointments and take their medicine. The trial is looking at this psychosocial component with a questionnaire evaluating the types of support systems that adolescents have to help them through their treatment.

Other factors such as insurance can also play a role. According to Bleyer and others, the least-insured age group in the U.S. comprises 8- to 30-year-olds. Young adults who get dropped from their parents’ insurance either can’t get insurance or aren’t motivated to do so. If so, they may be dropped from the pediatric regimen.

“I see this day in and day out in my clinic,” said Kantarjian, chair of the leukemia department at M. D. Anderson. “As soon as patients don’t have insurance, pediatric oncologists don’t put them on the regimen because they can’t comply, and they put them on the adult regimen.” The health care reform bill that passed last winter may help solve this prob-

lem with the provision allowing young adults to stay on their parents’ coverage until age 26.

Although overlooked in the past, adolescents with ALL are the focus of this trial, and Stock remains cautiously optimistic that the pediatric regimen can increase their survival rate substantially. “If we can improve survival rates by 25%, it would be amazing,” said Stock. “That is what this is all about.”

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