

# Molecular science could further improve leukemia survival

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The dramatic increase that has occurred in the cure rate for children with acute lymphoblastic leukemia (ALL) will be difficult to replicate in older patients without considerable additional research, according to an article by St. Jude Children's Research Hospital authors that appears in the March 22 issue of the *Lancet*.

In order to raise the survival rate of adolescents and adults with ALL, researchers will need a more thorough understanding of the biology of this form of leukemia, including the role that genes play in therapies, according to Ching-Hon Pui, M.D., chair of the St. Jude Department of Oncology and a leading ALL researcher. Currently, adolescents treated for ALL do not fare as well as children; and among adults with ALL, only 30 to 40 percent are cured.

Cure rates for children with ALL—defined as 10 years of cancer-free survival—were about 4 percent when St. Jude opened its doors in 1962; but by the end of that decade researchers showed for the first time that treatments using a combination of existing cancer drugs significantly improved ALL survival. Subsequent research at St. Jude contributed in large part to the current high cure rate achieved in children with ALL over the past four decades

ALL is characterized by an abnormal growth of immune-system cells called lymphocytes. About 5,400 new cases will be diagnosed in the United States in 2008, 60 percent of them in children up to age 18. The peak age of diagnosis is 2 to 5 years.

Today, pediatric ALL patients at St. Jude have a cure rate approaching 90 percent, Pui said. “We already have 94 percent surviving at 5 years.”

In “The Lancet” article, Pui and his colleagues noted that researchers are investigating two areas of molecular science that hold promise for improving the survival and quality of life of ALL patients, including adolescents and adults.

One is gene-expression profiling, which measures the amount of messenger RNA made by different genes in different cell types; and the other is pharmacogenetics. RNA is the decoded form of genes and is a signal that those genes have been active. Pharmacogenetics is the study of how genes influence a person’s responses to drugs.

Although still in the research phase, profiling a cell’s RNA can identify the major subtypes of ALL and pinpoint genes or chemical signaling pathways that play a role in determining a patient’s outcome.

“Gene expression profiling will help us identify targets for future therapy,” Pui said. “It is still crude, but in the end, you identify multiple genes for further study. If you find a good target for therapy, the next step is to develop molecular therapeutics for the target.”

Even a slight change in a gene may affect the efficacy and toxic side effects of cancer drugs. Originally, researchers focused on the influence of single genes. Now they seek to learn how the combination of gene variations within a cell affects treatment.

“Pharmacogenetics is important to finding out a person’s response and tolerance for a therapy,” Pui said. “Certain drugs may be good for 99 percent of patients but bad for 1 percent. We need to find out who those patients are who are at risk so we can spare them from toxicity.”

For instance, a genetic alteration affects an enzyme called thiopurine methyltransferase. Children with this alteration cannot metabolize a certain anti-cancer drug, and the active metabolite of the drug can accumulate in the body until it reaches toxic levels. About 10 percent of patients inherit one normal gene and one altered (non-functioning) gene for the enzyme, and one in 300 inherit two non-functioning versions of the gene.

Half of those with the one altered gene and all of those with two altered genes develop low blood cell counts when treated with regular dose of the drug, which can prove fatal in those with two altered genes. Determining the gene status of ALL patients can alert physicians to this risk. The physicians can then lower the treatment dose accordingly.

Some ALL specialists envision a time when oncologists use leukemic cell genetics and host pharmacogenetics to match specific treatments to individual patients.

“We need to know the leukemic cell genetics that affect drug sensitivity or resistance and what role pharmacogenetics plays in treatment to improve efficacy and decrease toxicity,” Pui said. “That way, we don’t over treat low-risk patients or under treat high-risk patients.”

Source: St. Jude Children's Research Hospital

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