Blincyto Boosts Chemotherapy as Initial Treatment for Some Kids with Leukemia

Adding blinatumomab to chemotherapy now represents a new standard for most children with standard-risk acute lymphoblastic leukemia.

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The immunotherapy drug blinatumomab (Blincyto) is already a standard treatment for some people with acute lymphoblastic leukemia (ALL). Following positive results from a large clinical trial, it's now expected to become part of the standard initial treatment for many children with the disease.

The trial, supported by NCI, included more than 1,400 children between the ages of 1 and 10 who were newly diagnosed with B-cell ALL. All of the children had what is called standard-risk ALL, meaning that the cancer did not have features that put them at an increased likelihood of their cancer coming back, or relapsing, after initial treatment. About 60% of children diagnosed with B-cell ALL have standard-risk disease.

Children in the trial treated with the combination of blinatumomab and a standard chemotherapy regimen had a substantial improvement in disease-free survival in comparison with children who only received chemotherapy. At a median of 2.5 years of follow-up, the disease-free survival rates in the two groups were 96% and 88%, respectively.

Disease-free survival is the length of time after starting treatment before any one of three events occur: the cancer returning (relapse), the diagnosis of a second (different) cancer, or death. In the trial, the improvement in disease-free survival was due almost entirely to there being far fewer relapses among children who received blinatumomab, explained Rachel Rau, M.D., of Seattle Children's Hospital and an investigator on the study.

Dr. Rau presented the findings December 7 at the annual meeting of the American Society of Hematology (ASH). They were published the same day in the New England Journal of Medicine.

Adding blinatumomab to chemotherapy now "represents a new standard for most [children] with standard-risk ALL," she said. The treatment was also safe, Dr. Rau reported. Most side effects were mild and could be managed with standard approaches.

With these new results and the June 2024 FDA expanded approval of blinatumomab, the drug should now be part of the go-to initial treatment for most children with the disease, explained Malcolm Smith, M.D., of NCI's Division of Cancer Treatment and Diagnosis.

But it's not recommended for use in children diagnosed with favorable-risk disease, Dr. Smith cautioned. These children are very likely to be cured with standard chemotherapy alone, he continued, so the "potential benefit that might be gained" from adding blinatumomab is extremely small.

Moving the needle on cure rates for kids with standard-risk ALL

B-cell ALL is the most common childhood cancer and has the highest cure rate among childhood cancers, at around 90%. But that figure has been largely static for nearly 2 decades, explained André Baruchel, M.D., an expert on treating childhood blood cancers at the Hôpital Universitaire Robert-Debréin Paris.

The high rate of cures came about "using old drugs, most of them available since the mid-1970s," Dr. Baruchel said during a presentation of the trial's findings at the ASH meeting.

The lack of progress has not been for lack of effort, he stressed. Many trials over the past 20 years have tried different approaches, including making treatments more intensive by adding additional drugs or using higher drug doses. But that approach "doesn't seem to work," he said.

Blinatumomab, a type of immunotherapy drug known as a bispecific T-cell engager, is the first immunotherapy drug found to improve how long children with B-cell ALL live without their cancer returning. It was initially approved to treat B-cell ALL nearly a decade ago, but until recently its use has largely been in people with relapsed disease.

In children with standard-risk disease, multidrug chemotherapy has long been the standard initial treatment throughout the different phases of treatment (e.g., induction and maintenance).

According to Dr. Rau, though, chemotherapy drugs have been the workhorses for far too long.

"We have reached the ceiling" of what can be achieved with chemotherapy, she said. "To really move the needle any further," she continued, drugs that work entirely differently than chemotherapy and that don't make chemotherapy's side effects any worse are needed.

Given its effectiveness in children and adults with high-risk B-cell ALL, and that it recruits the immune system to help kill cancer cells, blinatumomab fit that bill, she said.

Fewer relapses with blinatumomab, no safety concerns

The trial—called AALL1731 and conducted by the NCI-funded Children's Oncology Group—included children treated at hospitals across the United States as well as in Canada, Australia, and New

Zealand. It was also partly funded by Amgen, blinatumomab's manufacturer, and the St. Baldrick's Foundation.

The median age of participants was about 4 years old. All participants had standard-risk B-cell ALL and received standard chemotherapy-based induction and consolidation therapy. Based on how their cancer responded to that treatment—which included an assessment of remaining cancer cells in the bone marrow, known as minimal residual disease (MRD)—they were again categorized as being at favorable, average, or high risk of relapse.

With some exceptions, those at average and high risk were then randomly assigned to one of the two treatment groups. For those in the blinatumomab group, the two rounds of treatment with blinatumomab were interspersed with blocks of chemotherapy treatment beginning after completion of consolidation therapy. Each round of blinatumomab requires a 28-day continuous infusion.

The trial was stopped early after an early review of the results, known as an interim analysis, showed that disease-free survival in the blinatumomab–chemotherapy group was so much better than in the chemotherapy-only group that no more participants should be assigned to chemotherapy alone.

The difference in relapses between the two groups was substantial, Dr. Rau noted. In children with average relapse risk, for example, an estimated 2.5% of patients treated with blinatumomab had a relapse within 3 years, compared with nearly 10% in the chemotherapy group. In high-risk patients, those figures were about 4% and 14%, respectively.

And blinatumomab appeared to work very well even in patients with factors associated with a higher risk of relapse, including the presence of genetic features linked to worse responses to standard treatments. These findings, Dr. Rau said, suggest that blinatumomab is "capable of neutralizing" many of the molecular features of ALL that have traditionally been linked to a higher risk of relapse.

Given the results, Dr. Smith said, some of these so-called prognostic factors "may no longer be applicable" because they were determined during a period when chemotherapy alone was the standard treatment. But more research is needed to better understand which are no longer applicable and "whether any new factors that can reliably predict the risk of relapse may emerge."

Most children who received blinatumomab didn't have any serious side effects, including a potentially serious immune-related side effect called cytokine release syndrome, or CRS.

Children being treated with blinatumomab are carefully monitored for CRS, particularly in the first few days of treatment, explained Teresa York, M.D., who specializes in treating blood cancers at the University of Maryland Children's Hospital.

CRS "can mimic sepsis," Dr. York explained, "so it can be very scary." There are proven treatments to control CRS, she continued, but the goal is to recognize it as soon as possible.

Dealing with a 28-day infusion

Even with these practice-changing findings, there are still important questions to answer and issues to address, Dr. Rau said.

In the near term, one of the biggest challenges is the nearly month-long infusion period, which can "be a major barrier" for some children, such as those living in rural areas. So, the highest priority will be making blinatumomab as easy to access as possible.

"These results are really exciting, but if we can't get blinatumomab to every patient who might benefit from it, I think we've fallen short of our goals," she said.

After the first few days of the infusion, the child can finish the infusion at home as long as they aren't having any serious side effects, Dr. York explained. In some cases, home health care providers can assist with the infusions, she said, while in many other cases "we train the parents on how to manage it."

In a recent survey of hospitals affiliated with the Children's Oncology Group, in fact, the vast majority reported that most children having blinatumomab treatment left the hospital in 7 days or less, receiving the remainder of their treatment at home. Some smaller hospitals, however, reported that all children getting the drug remained in the hospital the entire 28-day period.

There is hope that this lengthy infusion may soon not be needed, however. Amgen has developed a formulation of the drug that can be given as an injection, with initial studies suggesting it is safe and as effective as the infusion.

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