Brentuximab May Mean Less Radiation for Children, Teens with Hodgkin Lymphoma

The new findings are an important first step in moving toward using even less radiation to treat high-risk pediatric Hodgkin lymphoma.

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For some children and teens with Hodgkin lymphoma, it may be possible to reduce or eliminate the need for radiation to treat their advanced cancer.

In a new study, researchers replaced one chemotherapy drug in a treatment regimen with the targeted therapy brentuximab vedotin (Adcetris) as the initial treatment of children and teens with a high-risk form of Hodgkin lymphoma. The modified treatment was highly effective against the cancer, and greatly reduced study participants' need for radiation therapy.

In the study, brentuximab was substituted for the chemotherapy drug vincristine in an established initial, or first-line, treatment regimen for high-risk pediatric Hodgkin lymphoma. The regimen consists of combinations of several chemotherapy drugs followed by radiation therapy when needed.

All 77 patients enrolled in the study received brentuximab, which is already approved by the Food and Drug Administration (FDA) as a first-line treatment for adults with advanced Hodgkin lymphoma.

After a median follow-up of 3.4 years, only one patient had their cancer come back, or relapse, and was successfully treated with additional therapies. One patient died unexpectedly of a heart problem. These survival outcomes were better than those of pediatric patients with high-risk Hodgkin lymphoma treated with a vincristine-containing regimen in an unpublished previous study by the same research group, which was used as a comparison group—called a historical control group.

Notably, 27 (35%) of the 77 patients in the clinical trial did not need any radiation treatments. When radiation was needed, it was restricted to those areas of the body that still showed signs of cancer, and the radiation doses were reduced as much as possible.

Reducing the amount of radiation that healthy tissues are exposed to is especially important in

younger patients, said the study's lead investigator Monika Metzger, MD, MS, of St. Jude Children's Research Hospital. Radiation is a risk factor for developing long-term health problems, or late effects. These may include second primary cancers, "particularly breast cancer in women, but also other cancers," Metzger explained.

The new findings are an important first step in moving toward using even less radiation to treat high-risk pediatric Hodgkin lymphoma, Metzger said.

"This was a very well-done study that had great results compared with the historical control and is helping to push the science of Hodgkin lymphoma forward," said pediatric oncologist Christine Moore Smith, MD, of Vanderbilt University, who was not involved with the study.

The researchers also found that use of the modified treatment regimen was not limited by the occurrence of a side effect called peripheral neuropathy, which can cause pain and numbness often starting in the hands and feet. Peripheral neuropathy is one of the concerns of using brentuximab, Smith said.

Results of the study, which was funded in part by NCI and sponsored by Seattle Genetics, the maker of brentuximab, were published April 7 in the Journal of Clinical Oncology.

It's not yet clear if brentuximab should be a standard part of the first-line treatment of children and teens with high-risk Hodgkin lymphoma, Smith said.

Longer term results from this study as well as results of an ongoing NCI-funded Children's Oncology Group (COG) trial should provide a clearer answer to that question, she explained. The COG trial is testing brentuximab as part of a different combination of chemotherapy as a first-line treatment regimen for these patients.

Reducing Side Effects and Late Effects

Brentuximab is a type of drug called an antibody–drug conjugate and is given by intravenous injection. The antibody part of the drug recognizes a protein called CD30, which is often found at high levels on classical Hodgkin lymphoma cells (called Reed-Sternberg cells). When the antibody binds to CD30 on these cancer cells, it delivers the drug vedotin to the cell, which clogs up the machinery of cell division and leads to cell death.

Both brentuximab and vincristine target and disrupt microtubules—flexible tube-like structures inside cells that are needed for cell division and other processes. "But while vincristine attacks cells everywhere in the body, brentuximab selectively targets the classical Hodgkin lymphoma cell," Metzger explained.

Classical Hodgkin lymphoma, in which cancer cells form in the lymph system, is uncommon overall but is the most commonly diagnosed cancer in adolescents aged 15–19. It is less common in children younger than age 15.

Because survival rates for children as well as adults with Hodgkin lymphoma are generally high,

much of the current research focuses on reducing side effects that occur during and after treatment—sometimes decades later—while achieving survival at least as good as with current treatment regimens, Smith said.

Improved Survival Without Relapse

To investigate whether giving brentuximab with combination chemotherapy reduces the need for radiation therapy, Metzger and her colleagues enrolled high-risk Hodgkin lymphoma patients up to 18 years old at St. Jude and five other centers.

All 77 patients in the trial received two cycles of brentuximab, etoposide, prednisone, and doxorubicin, followed by four cycles of cyclophosphamide, brentuximab, prednisone, and dacarbazine. A total of 27 patients showed no signs of cancer after the first two treatment cycles, as assessed by both PET scans and CT scans, and did not receive radiation therapy. The remaining patients received radiation therapy that was targeted to lymph nodes that still contained cancer.

The 3-year overall survival rates in the brentuximab group and the historical control group were similar, while the 3-year event-free survival (defined as patients who were still living, whose disease did not progress or come back, and who did not develop a second cancer) was higher in the brentuximab group.

The difference in event-free survival between the earlier study and the new study "is impressive," Smith said.

Trial participants tolerated the treatment well overall, and the most common serious side effects that occurred during treatment were low blood counts. However, the researchers noted, the death of one participant during the trial is concerning and warrants continued safety monitoring of brentuximab in all patients receiving the drug.

Low Levels of Neuropathy and Other Treatment-Related Pain

Only 4% of patients in the study had severe neuropathy or other pain during treatment. Severe neuropathy can require a change in chemotherapy, Smith noted. But that wasn't necessary in this trial, which she said was very encouraging for the future use of brentuximab in first-line treatment.

Peripheral neuropathy is a known side effect of vincristine, and it occurred more frequently among children in a German trial who received the established chemotherapy regimen that includes vincristine than in the current trial, Metzger said. However, a side-by-side comparison of side effects with the two regimens (one with vincristine, the other with brentuximab) has not been done.

Metzger and her colleagues are continuing to follow patients in the study to assess the 5-year overall survival and event-free survival with the new regimen.

Relapses of Hodgkin lymphoma are uncommon among patients who remain disease free 5 years

after treatment, and even more unlikely after 10 years, Metzger said.

Treatments Continue to Evolve

Future avenues of investigation should include “thinking about other ways we can reduce chemotherapy or radiation and decrease the late effects [of treatment],” Smith said.

“It’s fantastic that patients [in this trial] had an event-free survival rate of 97%,” she continued. “We want 100% of our patients to survive, but we also want them to survive with the highest quality of life possible,” Smith concluded.

Indeed, Metzger said, each clinical trial for pediatric Hodgkin lymphoma is designed to improve upon the results of the previous one.

“We have learned in this trial that we can omit radiation [for some children], and in the next trial, which is already underway, we’re omitting radiation in even more patients,” she continued. The new trial will also omit the steroid prednisone—which has its own side effects—for patients who respond well to the first two treatment cycles, she said.

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