Addition of Immunotherapy Boosts Pediatric Cancer Survival in Children with Neuroblastoma

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Administering a new form of immunotherapy to children with neuroblastoma, a nervous system cancer, increased the percentage of those who were alive and free of disease progression after two years, according to researchers at the University of California, San Diego School of Medicine and fellow institutions.

The percentage rose from 46 percent for children receiving a standard therapy to 66 percent for children receiving immunotherapy plus standard therapy, according to the study published in the Sept. 30, 2010 issue of the *New England Journal of Medicine*.

"This is the first clinical trial to document that a combination of anti-cancer monoclonal antibody (mAb) with cytokines is an effective anti-cancer therapy," said Alice L. Yu, MD, PhD, study chair and Professor of Pediatric Hematology Oncology at Moores UCSD Cancer Center. "This is also the first time a mAb targeting a glycolipid is shown to be effective for cancer immunotherapy since all therapeutic anti-cancer mAbs previously approved by FDA are directed against protein antigen. Overall, these findings present a clear paradigm shift and establish immunotherapy as a cornerstone to high-risk neuroblastoma treatment. This immunotherapy regimen will now be standard of care for children in first remission."

Neuroblastoma is a cancer of the peripheral nervous system (found outside of the brain and spinal cord), and is responsible for 12 percent of all deaths due to cancer in children under 15 years of age. It is the most common non-brain solid tumor in children. Nearly 50 percent of patients with neuroblastoma have a high-risk form of the disease and have poor long-term survival despite very intensive treatment.

The previously established standard treatment for neuroblastoma uses high doses of chemotherapy to destroy as many cancer cells as possible. But this form of chemotherapy (myleoablative therapy) also destroys some normal blood-forming cells, so it is followed by giving back previously collected blood-forming cells to restore immune system function and blood cell formation. Patients who respond to this therapy are then given a derivative of vitamin A to further treat any remaining cancer cells. More than half of the patients with high-risk neuroblastoma treated in this manner succumb to the disease.

A newer approach to cancer treatment is immunotherapy, which in this instance uses an antibody called ch14.18 to target a substance on the surface of tumor cells called GD2. The GD2 is expressed by cancers such as neuroblastoma but is also present on some normal nerve cells. Early-phase studies demonstrated the safety and activity of ch14.18 when it was given with other drugs that boost the immune system. Those drugs include a factor which stimulates white blood cell growth and a hormone that increases the number and activity of certain types of immune cells.

In this study, 226 children with high-risk neuroblastoma who had responded to myeloablative therapy were randomly assigned to receive standard therapy (isotretinoin), or isotretinoin, ch14.18, and the immune system boosting drugs. The median time these patients were followed in the study was approximately two years. Although the original plan had been to compare outcomes after three years, the study stopped early because

of the strongly positive results, allowing those on standard therapy to switch to ch14.18 immunotherapy if they wished.

Toxicities, including pain, low blood pressure, capillary leak and hypersensitivity reactions, were encountered with the immunotherapy treatment at a significantly greater rate than compared to those who just received the standard therapy. However, side effects in the immunotherapy group were temporary and primarily resolved when treatment was stopped.

The randomized phase III clinical trial was coordinated by the Children's Oncology Group (COG), a national consortium of researchers supported by the National Cancer Institute (NCI), part of the NIH.

Because there was no pharmaceutical company to make ch14.18 when the phase III trial started, NCI manufactured the agent and provided it to COG for the clinical trial. NCI continues to manufacture ch14.18 and to make it available to children with high-risk neuroblastoma through ongoing Children's Oncology Group clinical trials. NCI has identified a pharmaceutical partner, United Therapeutics Corp., Silver Spring, Md., that will eventually take over responsibility for manufacturing ch14.18 and which will be responsible for obtaining U.S. Food and Drug Administration approval of ch14.18 for the treatment of high-risk neuroblastoma.

Fellow researchers included Andrew L. Gilman, MD, M. Fevzi Ozkaynak, MD, Wendy B. London, PhD, Susan G. Kreissman, MD, Helen X. Chen, MD, Malcolm Smith, MD, PhD, Barry Anderson, MD, Judith G. Villablanca, MD, Katherine K. Matthay, MD, Hiro Shimada, MD, Stephan A. Grupp, MD, PhD, Robert Seeger, MD, C. Patrick Reynolds, MD, PhD, Allen Buxton, MS, Ralph A. Reisfeld, PhD, Steven D. Gillies, PhD., Susan L. Cohn, MD, John M. Maris, MD, and Paul M. Sondel, MD, PhD, for the Children's Oncology Group.

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