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Immunotherapy shows promise in Phase III neuroblastoma trial

Results of a Phase III clinical trial presented at the 2009 American Society of Clinical Oncology meeting (*J. Clin. Oncol.* **27**, S15; 2009) show that an antibody-based immunotherapy increased event-free survival of patients with high-risk neuroblastoma by 20%.

Neuroblastoma is a cancer of the nervous system that is difficult to treat and largely afflicts young children. Current treatment for high-risk neuroblastoma is based on surgery, intensive chemotherapy with stem cell rescue and radiation therapy. However, the disease often returns and only ~30–40% of patients survive. As Alice Yu, Professor of Paediatric Haematology and Oncology at the University of California in San Diego and the Moores Cancer Center, and lead author of this study, points out: "There has been no improvement in the outcome since the benefit of bone marrow transplant followed by isotretinoin was demonstrated a decade ago". There is therefore a clear need for novel approaches.

Yu and colleagues evaluated an immunotherapy regimen based on a chimeric monoclonal antibody (mAb) known as ch14.18. It targets GD2 — a glycolipid expressed on neuroblastoma cells that inhibits the immune system from attacking cancer cells — and induces antibody-dependent cell-mediated cytotoxicity (ADCC) towards GD2-expressing tumour cells. The mAb was combined with granulocyte–macrophage colony stimulating factor (GM-CSF) and interleukin 2 (IL-2), as previous studies have shown that such immunomodulators can improve the anticancer efficacy of mAbs by increasing the number and activity of effector cells.

In the trial, which involved 226 patients who had been newly diagnosed with high-risk neuroblastoma, immunotherapy added to a standard treatment regimen using isotretinoin was compared with standard treatment alone. After 2 years, event-free survival was 66% in the immunotherapy group versus 46% in the standard treatment group, and overall survival was 86% in the immunotherapy group versus 75% in the standard treatment group. As most (>90%) relapses occur in the first 2 years, this result reflects a significantly improved cure rate. The main side effects reported in the immunotherapy group included pain (21%), vascular leak syndrome (7%) and allergic reactions (7%). The use of narcotics and close monitoring with careful supportive care can help minimize these, says Yu.

Overall, "these findings present a clear paradigm shift and establish immunotherapy as a cornerstone of high-risk neuroblastoma treatment. This immunotherapy regimen will now be standard of care for children in first remission," says John J. Maris, Director of the Cancer Center at The Children's Hospital of Philadelphia. "The biggest challenge for the paediatric oncology community is that the antibody is in limited supply and no commercial partner has been identified."

In addition to demonstrating the benefits of combining IL-2 and GM-CSF with a mAb for the treatment of cancer, "this is the first time a mAb targeting a glycolipid is shown to be effective," says Yu. Currently, all FDA-approved mAbs or vaccines for cancer are directed against protein antigens. As GD2 is overexpressed in malignant melanoma, osteosarcoma and small-cell carcinoma of the lung, these findings suggest that this immunotherapeutic strategy could be applied to other types of cancer.