Trial watch

IMPROVED CHEMOTHERAPIES

Neuroblastoma is characterized by poor long-term survival as tumours normally relapse and disseminate after chemotherapy in more than 50% of the patients. A system of risk stratification established for this heterogeneous disease has helped to tailor chemotherapy to minimize therapeutic side effects, which can severely affect quality of life, and improve outcome. Data from two Phase III clinical trials published in the *New England Journal of Medicine* show possible ways to further improve survival rates for patients with intermediate and high-risk neuroblastoma.

In preclinical studies, the inhibition of the tumour-associated antigen disialogangliside 2 (GD2) by a chimeric human-mouse antibody (ch14.18) has shown activity in neuroblastoma, suggesting that GD2-specific antibodies are good candidates for immunotherapy. The activity of ch14.18 can be enhanced when combined with granulocyte–macrophage colony-stimulating factor (GM–CSF) or interleukin-2 (IL-2). This formed the basis of a Phase III study in which 252 patients with high-risk neuroblastoma, 226 of whom had previously responded to myeloablative therapy and stem-cell transplantation, were randomly assigned to different treatment groups. Half of these patients received standard therapy (six cycles of isotretinoin) and the other half of the patients received immunotherapy (five cycles of ch14.18 in combination with GM–CSF and IL-2, and a dose of isotretinoin at the end of each cycle). This group showed an improved overall survival rate compared with the standard therapy group (86% compared with 75%) despite considerable toxic side effects that were related to the immunotherapy regimen; these included pain, hypotension, capillary leak syndrome and hypersensitivity reactions.

The Children's Oncology Group conducted another Phase III trial, to assess whether a reduction in the dose and duration of standard chemotherapy could be equally effective in maintaining the current 3-year overall survival rate of 90% in patients with intermediate-risk neuroblastoma. The 479 patients with different stages of neuroblastoma were enrolled and assigned to two groups — favourable and non-favourable — according to the histopathological features of the tumour. The 323 patients who were diagnosed with favourable biological features received four cycles of carboplatin, etoposide, cyclophospamide and doxorubicin, which was a 70% reduction in the duration of the therapy compared with regimens used in earlier trials. The 141 patients with non-favourable biological features received eight cycles of the same chemotherapy combination (a reduction of 40%). A 3-year overall survival rate of 96% for the entire group (98% for patients with favourable features and 93% for patients with non-favourable features) was achieved.

These studies present different approaches to increase the efficacy of two established regimens that combat neuroblastoma and underline the importance of refining risk stratification to find an adequate therapy for this disease.

ORIGINAL RESEARCH PAPERS Baker, L. B. *et al.* Outcome after reduced chemotherapy for intermediate-risk neuroblastoma. *N. Eng. J. Med.* **363**, 1313–1323 (2010) | Yu, A. L. *et al.* Anti-GD2 antibody with GM-CSF, interleukin-2 and isotretinoin for neuroblastoma. *N. Eng. J. Med.* **363**, 1324–1334 (2010)