Abstract

Chemotherapy-induced neurotoxicity can reduce the quality of life of patients by affecting their intelligence, senses and mobility. Ten percent of safety-related late-stage clinical failures are due to neurological side effects. Animal models are poor in predicting human neurotoxicity due to interspecies differences and most in vitro assays cannot distinguish neurotoxicity from general cytotoxicity for chemotherapeutics.

We developed in vitro assays capable of quantifying the paediatric neurotoxic potential for cytotoxic drugs. Mixed cultures of human fetal brain cells were differentiated in monolayers and as 3D-neurospheres in the presence of non-neurotoxic chemotherapeutics (etoposide, teniposide) or neurotoxicants (methylmercury). The cytotoxic potency towards dividing progenitors versus differentiated neurons and astrocytes was compared using: (1) immunohistochemistry staining and cell counts in monolayers; (2) through quantitative Western blots in neurospheres; and (3) neurosphere migration assays. Etoposide and teniposide, were 5–10 times less toxic to differentiated neurons compared to the mix of all cells in monolayer cultures. In contrast, the neurotoxicant methylmercury did not exhibit selectivity and killed all cells with the same potency. In 3D neurospheres, etoposide and teniposide were 24 to 10 times less active against neurons compared to all cells. These assays can be used prioritise drugs for local drug delivery to brain tumours.