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Peripheral neurotoxicity of platinum-based chemotherapy

Guido Cavaletti

Dipartimento di Neuroscienze e Tecnologie Biomediche, Università di Milano Bicocca, Via Cadore 48, 20052 Monza, Italy. e-mail: guido.cavaletti@unimib.it

The review by Kelland (Kelland, L. The resurgence of platinum-based cancer chemotherapy. *Nature Rev. Cancer* **7**, 573–584 (2007))[1] is an extensive review of the current knowledge on platinum-based chemotherapy, focused both on toxicity and anticancer cell activity. However, the clinical importance of a major toxic side effect of the currently available platinum drugs, that is, peripheral neurotoxicity, is under-represented. This is surprising, as platinum-induced sensory neuropathy can be a dose-limiting toxicity[2,3] and despite extensive efforts we are still unable to prevent or treat it[4,5], as evidenced by the significant number of ongoing neuroprotection clinical trials focused on chemotherapy-induced peripheral neurotoxicity (for a detailed, although only partial, list see the United States National Institutes of Health website ClinicalTrials.gov).

The severe and disabling sensory peripheral neurotoxicity of platinum-derived drugs is mainly due to anatomical factors. In fact, platinum drugs are almost completely unable to cross the intact blood–brain barrier, but they have an easy access to less efficiently protected areas of the nervous system, such as the dorsal root ganglia where the primary sensory neurons are located. It has been clearly demonstrated in animal models that platinum accumulates at this site and exerts its neurotoxic effect through a still unknown mechanism[6–12]. Moreover, during anticancer chemotherapy it is also possible that interaction of platinum drugs with other co-administered neurotoxic compounds occurs in dorsal root ganglia, with unpredictable effects on neurons[13].

Although the general toxicity profiles of cisplatin, carboplatin and oxaliplatin are different (for instance, oxaliplatin is not nephrotoxic and carboplatin is more severely myelotoxic than the other compounds), all these drugs damage the peripheral nervous system to a different extent, and the use of high-dose regimens is prevented by their neurotoxicity[2,14–16]. Overall, the experimental data in animal models of chemotherapy-induced peripheral neurotoxicity are in agreement with the currently available results in humans[2] and suggest that the probable mechanisms of the antineoplastic activity of platinum drugs are not the same as those involved in their neurotoxicity. This might offer the scientific basis to achieve an effective, clinically relevant reduction of platinum-drug neurotoxicity without any interference with the activity of the compounds against cancer cells.

The current strategies in neuroprotection clinical trials are based either on symptomatic treatment using antiepileptic or pain-killer drugs, such as pregabalin, lamotrigine and gabapentin, or on the administration of antioxidants (for example, α-lipoic acid and vitamin E), detoxicants (for example, dimesna and amifostine), growth factors or growth-factor modulators (for example, erythropoietin, acetyl-L-carnitine and xaliproden). However, it should be acknowledged that these trials, as well as all the others previously performed in chemotherapy-induced peripheral neurotoxicity, although generally based on promising preclinical results obtained in animal models[17], have been so far unable to obtain a clinically relevant prevention of the onset of disabling sensory symptoms, or to treat them.

In the absence of effective neuroprotection strategies, it is the general experience that a large proportion of patients that are treated with chemotherapy schedules including cisplatin or carboplatin develop a potentially severe peripheral neurotoxicity with sensory symptoms and signs (especially ataxia) that can permanently impair the patient's quality of life. The relevance of this side effect is further highlighted by the frequent occurrence of the 'coasting' phenomenon in platinum-treated patients, who experience worsening of their symptoms for months despite drug withdrawal. Recovery is frequently incomplete and it can take months or years. Moreover, chronic sensory impairment (and not the acute, reversible, cold-related sensory symptoms occurring after each cycle of chemotherapy[1]) represents the truly clinically relevant side effect, causing drug withdrawal in oxaliplatin-treated patients, although less frequently than in cisplatin or carboplatin treatment[18].

For these reasons I believe that all the physicians and researchers involved in the care of cancer patients or in the development of new platinum-based drugs should be fully aware of the potential severity and irreversibility of the damage to the peripheral nervous system induced by treatment and unite their efforts to develop an effective neuroprotective strategy.

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