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Commentary

Calcium and Magnesium Prophylaxis for Oxaliplatin-Related Neurotoxicity: Is It a Trade-off Between Drug Efficacy and Toxicity?

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The improvement in the treatment of cancer patients achieved by oncologists over the last decades allowing longer survival times associated with the more effective management of several major side effects of antineoplastic chemotherapy (e.g., myelosuppression and emesis) permitted other toxicities to emerge as clinically relevant issues. At the same time, the greater number of long-term cancer survivors indicates the need for an even more serious consideration of the quality of life of these patients [1, 2], with rigorous attempts to quantify its impairment and to improve it through different pharmacological and nonpharmacological approaches. With this background, chemotherapy-induced peripheral neurotoxicity (CIPN) represents one of the most serious side effects experienced by patients treated with platinum drugs, taxanes, vinca alkaloids, epothilones, bortezomib, and thalidomide [3, 4]. In fact, all these drugs used to treat a wide spectrum of solid and hematological malignancies can induce severe CIPN in a proportion of cancer patients, and its severity can be dose-limiting [5].

Several attempts to prevent or treat CIPN have been performed in the past years, but the results were conflicting and overall inconclusive. Besides drug inefficacy, other reasons for these unsatisfactory results should be considered, including poor rationale, methodological flaws in trial design and conduction, and the use of inappropriate outcome measures.

The paper by Khattak [6] gives scholarly evidence of this situation, revising the unsettled issue of the use of calcium–magnesium solution to prevent oxaliplatin-induced CIPN [7]. Oxaliplatin, the third platinum drug entered in clinical practice after the first-in-class cisplatin and its derivate carboplatin, is an effective compound largely used to treat colorectal cancer. From a neurotoxicity standpoint, it is remarkable that, despite evident structural differences, oxaliplatin shares with the more neurotoxic cisplatin the clinical features of typical dose-dependent sensory neuropathy with distal numbness and paresthesias associated with potentially severe ataxia. However, oxaliplatin use is also associated with a unique form of cold-dependent acute neurotoxicity affecting almost all treated patients and represented by a tingling sensation with a predominant perioral, pharyngeal, and finger localization associated with muscle cramps [8]. Based on this clinical evidence, the use of calcium–magnesium infusion has been proposed as a possible treatment for CIPN in oxaliplatin-treated patients, although frequently the treatment target, that is, acute or chronic CIPN or both, was unclear. In spite of the safety concern previously raised by some investigators, it is now accepted that calcium–magnesium infusion is a reasonably safe procedure in oxaliplatin-treated patients, but it is still without established effectiveness against CIPN.

The pathogenesis of CIPN in oxaliplatin-treated patients has not yet been completely clarified, thus preventing a solid and rationale-based approach for its prevention and treatment [9, 10]. At present, it is my understanding that the role of platinum-DNA binding is likely to be highly relevant in the onset of chronic symptoms and signs whereas electrolyte imbalance with altered activity of calcium-dependent sodium channels secondary to oxalate chelating activity might be a major determinant of acute CIPN. However, it has also been suggested that this latter effect is relevant to the development of chronic CIPN.

A second major issue, clearly identified by Khattak [6] in most of the studies that attempted to investigate the protective role of calcium–magnesium infusion, is the lack of a sound trial design. In fact, he correctly criticized the use of underpowered studies, retrospective analyses, and unblinded observations, as well as the lack of proper controls and the evaluation of nonhomogeneous series of patients (e.g., adjuvant and palliative treatments).

Another frequently underestimated but highly relevant un-

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settled issue is represented by the selection of appropriate outcome measures to assess the severity of CIPN in clinical trials and, therefore, to evaluate the extent and clinical relevance of a putative neuroprotective treatment. In most oncological clinical trials, toxicities are assessed using common toxicity criteria (CTC) scales, the most widely used being the National Cancer Institute (NCI)-CTC in its different versions [11]. However, although for several toxicities (particularly those unequivocally measurable such as, for instance, myelotoxicity) the NCI-CTC are adequate, their usefulness for CIPN is questionable because its results are frequently difficult to reproduce because of subjective interpretation of the scale items, leading to possible under- or overevaluation of the severity of CIPN [12, 13]. To overcome this established limitation, several drug-specific scales have been developed to assess the severity of CIPN in oxaliplatin-treated patients, but they do not really contribute to solving the problem. For instance, a questionnaire was developed by Leonard et al. [14] to be filled out by a research nurse during an interview with patients queried about symptoms occurring in the upper and lower extremities and in the orofacial zone. Patients had to separately assess the severity of the symptom and the effect on daily activities of acute CIPN, but the validity of the questionnaire was never formally assessed. This is also true for the oxaliplatin-specific questionnaire described by Lévi et al. [15], for which the interpretation of the results is further complicated by the coexistence of items describing the duration of symptoms (without any descriptive discrimination between acute and chronic toxicity) and their impact on functional activities.

The absence of a validated outcome measure for CIPN (either based on physical examination or patient reported) is an unmet clinical need not only in oxaliplatin-treated patients but also in general in the population of patients treated with neurotoxic anticancer drugs. In fact, this absence prevents the careful assessment of patients exposed to neurotoxic chemotherapy, but it also affects the accuracy of the trials designed to explore the efficacy of neuroprotective substances. This observation is supported by the analysis of the literature data and it was clearly evidenced during a CIPN workshop held at the National Institutes of Health (Bethesda, MD) on June 24, 2011, during which a wide panel of U.S. and European oncologists, neurologists, pain specialists, and basic researchers discussed the issue.

In this context, a large international academic trial involving several U.S. and European oncological centers—the Chemotherapy-Induced Peripheral Neuropathy Outcome Measures Standardization (CI-PERINOMS) study[16]—recently completed the enrollment of >280 patients with CIPN who were examined with an extended series of scales and questionnaires to assess their reliability and validity, a critical step in the search for the optimal method to detect and describe its features in daily practice and in clinical trials. In fact, until reliable, valid, reproducible, and responsive methods are used to properly assess CIPN, any effort to establish an effective neuroprotection treatment will be unrealistic.

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