Chapter 11

Nutraceuticals for Prevention of Chemotherapy–Induced Peripheral Neuropathy

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**ABSTRACT**

A wide range of neurologic complications, including central neurotoxicity conditions and peripheral neurotoxicity, are associated with antineoplastic drug regimens. Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most common and severe cancer treatment-related adverse effect, as well as the most diffuse type of neurotoxicity, because about one third of all patients who undergo chemotherapy may experience this side effect. CIPN can negatively impact the long-term quality of life of cancer survivors, and can lead to dose reduction of the chemotherapy agent, or possible cessation of treatment. Unfortunately, although several agents and protocols have been proposed, no prophylactic strategies have proven useful yet. Therefore, new alternative therapies have been considered for CIPN prevention. In this chapter, the authors analyze the potential applications of nutrients, dietary supplements and herbal products, such as single herbs, the Kampo medicine goshajinkigan and other herbal combinations, for CIPN prevention.
INTRODUCTION

Neurologic dysfunction is a common side effect of many chemotherapy drugs and each part of the central or peripheral nervous system can be involved. It is of note that a wide range of neurologic complications are associated with antineoplastic drug regimens, such as central neurotoxicity conditions, ranging from minor cognitive deficits to encephalopathy with dementia or even coma, and peripheral neurotoxicity. This latter condition represents the most diffuse type of neurotoxicity. Because this type of neurotoxicity is due to the administration of anticancer drugs it is commonly indicated as chemotherapy-induced peripheral neuropathy (CIPN) which, clinically, ranges from minor, and temporary symptoms (e.g., paresthesia), to severe and permanent forms of polyneuropathy. Indeed, the term CIPN includes a wide range of clinical conditions with heterogeneity of causes and different clinical expressions.

Accumulating evidence indicates that many chemotherapy drugs are known to cause peripheral neuropathy (Cavaletti & Marmiroli, 2015). Among these drugs, platinum compounds, antitubulins (taxanes, vinca alkaloids, eribulin), and proteasome inhibitors (bortezomib) have a significant role in the genesis of CIPN, although other molecules such as immunomodulatory agents (thalidomide, lenalidomide, pomalidomide) can also cause peripheral neuropathy. In addition, etoposide, methotrexate, 5-fluorouracil (5-FU), gemcitabine are less commonly, or not associated with this complication, whereas the use of biological agents has been occasionally associated with CIPN.

Statistically, CIPN is a common treatment-related adverse effect, affecting up to 48% of cancer patients who received chemotherapy (Seretny et al., 2014), and about 92% of patients underwent to the drug combination FOLFOX (folinic acid, 5-FU and oxaliplatin) suffered by sensory CIPN (Denlinger & Barsevick, 2009). Consequently, this serious complication can negatively impact the long-term quality of life (QoL) of cancer survivors. Indeed, although CIPN is generally a temporary manifestation, a percentage up to 40% of patients with CIPN may experience permanent symptoms, such as paresthesia and other types of disability, after the end of the therapeutic course (Park et al., 2013; Smith, Cohen, Pett, & Beck, 2010). Moreover, a disabling form of painful CIPN can also persist from months to years after the chemotherapy conclusion, representing a permanent side effect and leading to a significant worsening of the QoL. Again, the occurrence of CIPN can lead to dose reduction of the chemotherapy agent, or possible cessation of treatment, which may have an adverse impact on cancer treatment and disease outcomes.

Although the prevention of this serious complication is of pivotal importance in oncology, at the moment very few options are available for this purpose. To date, there are no chemoprotective agents that have shown consistent clinically meaningful benefits for CIPN prevention whereas anti-seizure drugs, such as carbamazepine and pregabalin, and antidepressants (e.g., venlafaxine), are ineffective, or seem to have more results in the treatment of CIPN rather than in its prevention (Durand et al., 2012). Consequently, the proposed strategies concern the adoption of a stop-and-go regimen, the cumulative dose-reduction, or the use of lower dose-intensities.

After a brief overview on the pathophysiology and features of CIPN, the aim of this chapter is to dissect the role of natural products tested for the prevention of this side effect (Cascella, & Muzio 2017a). In particular, several natural compounds have been studied to evaluate their effectiveness against CIPN (Abad, Nouri, Gharjanie, & Tavakoli, 2011; Abad, Nouri, & Tavakkoli, 2011; Al Moundhri, Al-Salam, Al Mahrouqee, Beegam, & Ali, 2013; Amara, 2008; Arrieta et al., 2011; Cheng et al., 2015; Ghoreishi et al., 2012; Hershman et al., 2013; Kaur, Jaggi, & Singh, 2010; Kottschade et al., 2011; Lee et al., 2012; Liu et al., 2013; Loprinzi et al., 2014; Muthuraman, Singh, & Jaggi, 2011; Park et al., 2012; Schloss,

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