Chemotherapy-Induced Neuropathy and Diabetes

Subjects: Oncology

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Diabetes mellitus and cancer are among the four most common chronic diseases, and are two of the leading causes of death worldwide [1]. Treatment of cancer patients with chemotherapy is influenced by multiple aspects, including neuropathy induced by chemotherapy drugs their self.

Keywords: toxicity ; side effects ; cold sensitivity ; autonomic dysfunction ; regimens ; cytostatic drugs

1. Introduction

Chemotherapy-induced neuropathy is a significant source of morbidity in cancer patients, with high incidences (**Table 1**) and can be a dose-limiting side effect for many classes of chemotherapy drugs [1]. Diabetes mellitus is a commonly encountered comorbidity among patients with solid tumors [2][3][4]. Diabetes mellitus and its accompanying metabolic syndrome have been shown to correlate with the development and outcomes of a number of solid tumors [2][3][5]. Outcomes are often worse in cancer patients who also have diabetes [6]. It is well known that high blood glucose can damage peripheral nerves [7][8]; as such, patients with diabetes who are treated with chemotherapy drugs may be at greater risk of developing chemotherapy-related peripheral neuropathy [9]. Despite the high prevalence of neuropathy among cancer and diabetes patients, little is known about neuropathic symptoms among cancer patients with comorbid diabetes. Because peripheral neuropathy is commonly observed in patients with diabetes, most studies of chemotherapy-induced peripheral neuropathy exclude patients with diabetes [1]. An analysis of the trial E1199, which included 5052 patients with axillary node-positive or high-risk, node-negative breast cancer showed that patients who received adjuvant taxanes containing therapy, glycemic instability and obesity were associated with an increased risk of neuropathy. However, information regarding a pre-existing history of diabetes was not available in this study [10].

Table 1. Incidence of neuropathy induced by main classes of cancer chemotherapy drugs.

Class of Chemotherapy Drugs	Drug Name	Neuropathy Incidence (%) (Classified by Neurotoxicity Degrees)	Reported Neurotoxic Doses
Anthracyclines	Doxorubicin (Adriamycin)	75% (cognitive impairment "chemobrain") [11]	-
Taxanes	Paclitaxel	All grades: 60% [12] Grade 3–4 motor: 11% Grade 3–4 sensory: 33% [13]	1000 mg/m^2 cumulative dose [14]
	Docetaxel	All grades: 15% [12][15] Grade 3–4: 2% [15]	400 mg/m^2 cumulative dose [14]
Platinum-based agents	Cisplatin	Grade 1:14–33% Grade 2: 0–33% Grade 3: 2–19% Grade 4: 0–4% [16]	250–450 mg/m^2, and all patients develop neuropathy [16][17], at cumulative dose of 500–600 mg/m^2 [18]
	Oxaliplatin	Grade 1: 21–94% Grade 2: 5–42% Grade 3–4: 3–19% [16][19]	>550 mg/m^2 Severe neurotoxicity at cumulative dose of 750–850 mg/m^2 [20] Chronic neuropathy with a cumulative dose between 850 mg/m^2 and 1800 mg/m^2 [16]
	Carboplatin	All grades: 4–6% [21]	>400 mg/m^2 Neurotoxicity only with high doses or in combination with other drugs [17]

Class of Chemotherapy Drugs	Drug Name	Neuropathy Incidence (%) (Classified by Neurotoxicity Degrees)	Reported Neurotoxic Doses
Vinca alkaloids	Vincristine	Grade 1–2: 60% [12]	30–50 mg [12][17]
	Vinorelbine	All grades: 44% [22] Grade 3–4: ≈ 2% [23]	125 mg/m^2 [22]
Antimetabolites	5-fluorouracil (5-FU)	All grades: 0.6–7% [24][25] or 12.9% [26] Grade 3–4: 0% [26]	Uncertain [27] High doses and use of 5-FU in combined treatment, increase the risk of neuropathy [28]
	Gemcitabine	All grades: 6% [29]	-
	Methotrexate	All grades: 3–10% [28]	-

Although there is considerable evidence that patients with pre-existing symptoms of diabetic neuropathy or other types of neuropathies are at increased risk of developing a higher grade following chemotherapy with cytostatic agents [30], there are no published reviews on the effect of chemotherapy administration in diabetic patients who do not have neuropathy or the evolution of neuropathy during cancer treatment in diabetic patients. The incidence of chemotherapy-induced peripheral neuropathy depends largely on the type of agent used, the duration of treatment (number of chemotherapy cycles received) and the dose used. In the case of diabetic patients it has been postulated that the loss of axonal integrity due to decreased regeneration makes diabetic patients prone to neuronal toxicity from drugs such as chemotherapy [31].

Among the pharmacological agents that have the greatest ability to induce peripheral neuropathy in oncological patients, taxanes and platinum derivatives have been the most studied [32]. For example, in treatment with the oxaliplatin derivative, a drug widely used in colorectal and other cancers, neurotoxicity usually presents mainly as peripheral sensory neuropathy, which can become persistent and therefore can be a dose-limiting toxicity of oxaliplatin or even treatment discontinuation. Persistent peripheral sensory neuropathy is cumulative with doses received, and in the case of oxaliplatin for example, severe neuropathy (Grade 3 and 4) occurs in 10–20% of patients receiving total doses of this drug from >750–850 mg/m 2 [33]. Paclitaxel (taxanes family) induced peripheral neuropathy usually begins with paresthesia and numbness and is also cumulative and may result in patient functional impairment and limitation of use [34].

It is well known that diabetic patients with neuropathy have a lower quality of life, an increased risk of falls [35], and are at increased risk of ulcerations, which in turn can lead to lower extremity amputation [36]. Although in some cases symptoms may improve with appropriate glycemic control, a significant number of patients continue to experience neuropathic symptoms many years after the end of treatment [6].

2. Relationship between Chemotherapy, Neuropathy and Diabetes

The analysis reveals that most neuropathic symptoms or the onset of neuropathy occurs at an early stage [37] or at lower doses [1] in diabetic patients than in non-diabetic patients treated by chemotherapy. Moreover, among diabetic patients receiving chemotherapy, neuropathy rates were higher in patients with a longer duration of diabetes [38]. However, this deleterious effect was not associated with differences in cancer treatment including chemotherapy, which suggests that diabetes mellitus rather than chemotherapy could be responsible for these symptoms. In addition, the effects seem to last longer, since two years after treatment, peripheral neuropathy persisted in a higher proportion of diabetic patients than in non-diabetic patients (68.7% vs. 29.2%). Furthermore, it was a functionally significant peripheral neuropathy in 18.2% of the cases [34]. Since not all chemotherapeutic drugs have the same ability to cause peripheral neuropathy, the drugs investigated are chemotherapy drugs with a high potential to induce neuropathy, such as platinum compounds and taxanes, which are currently the mainstay of treatment for various common tumors. Clinical studies report incidences of neuropathy after chemotherapy of up to 60% with cisplatin, paclitaxel, docetaxel and oxaliplatin, among other drugs [39][40][41]. In particular, oxaliplatin, which is widely used in the treatment of colon cancer, causes acute and transient neurotoxicity in almost all patients treated, and subsides after about 48 h [16][42], and becomes chronic in a few cases [39]. Some of these studies mention that the risk of paresthesia is increased in diabetic patients during the first minutes of infusion [43] and development takes place in a shorter time or with lower cumulative doses compared with non-diabetic patients [1][37]. Future studies should evaluate the influence of the severity and duration of diabetes. As for acute chemotherapy-induced neurological symptoms, Abdel-Rahman (2018) [37], found no differences between diabetic and non-diabetic patients, although diabetic patients developed oxaliplatin-induced paresthesia in a shorter time. Vissers et al. (2015) [6] concluded that diabetic patients suffered a higher burden of neuropathic symptoms than non-diabetic patients, regardless of the antineoplastic treatment.

Subsequent studies that have also worked directly with the diabetic population have observed that diabetes acts as a risk factor in terms of the incidence and severity of peripheral neuropathy in those patients treated with chemotherapy [34][38]. Kus et al. (2016) [38] jointly evaluated the influence of taxanes and their combination with platinum derivatives and found that the incidence was higher in diabetic patients who received the combination of both agents. They also grouped patients by degree of hyperglycemia, but this did not show any difference in the development of peripheral neuropathy [38].

At present it is known that chemotherapy-induced neuropathy interferes with the quality of life and it is often accompanied by depressive symptoms and apathy and abandonment of leisure activities and physical activity [44][45][46]. It should be taken into account that the symptoms of neuropathy can last between two to eleven years after its diagnosis in more than half of the patients, where tingling and numbness affect 70% of the patients with chemotherapy-induced peripheral neuropathy [46] and those patients displaying higher neuropathy symptoms also showed a reduced quality of life after chemotherapy discontinuation as recently reported for taxanes in patients with breast cancer [47] and for oxaliplatin in colorectal cancer patients [48] or carboplatin/taxanes regimen in patients with gynecologic cancer survivors [49]. Regarding diabetic patients and chemotherapy-induced neuropathy in terms of health-related quality of life, the study by Visser et al. by using the European Organization for Research and Treatment of Cancer quality of life questionnaire—chemotherapy-induced peripheral neuropathy (EORTC QLQ-CIPN20) evaluated the differences in neuropathic symptoms between colorectal cancer patients with and without diabetes. Those with diabetes reported a decreased quality of life associated with higher impairment in sensitive symptoms such as tingling in fingers, hands, toes and feet, numbness, aching or burning pain in toes or feet, and trouble while standing or walking. In contrast, no differences were reported for neuropathic symptoms regarding motor symptoms or autonomic dysfunction except for getting or maintaining an erection in men [6].

Future studies investigating the risk of neuropathy in cancer patients with comorbid diabetes need to be analyzed considering the duration of diabetes, cancer-induced neuropathic effects per se, prior cancer management strategies such as radiotherapy and surgery, and the type and dose of chemotherapy used.

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