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Progressive paresthesias after cessation of therapy with very high-dose cisplatin

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Summary. Control of cisplatin-induced nephrotoxicity and nausea/vomiting has enabled the development of very high-dose cisplatin regimens (monthly total dose, 200 mg/m^2). Neurotoxicity is now recognized to be the dose-limiting toxicity of these regimens. However, during a pilot study involving 5 mg/m^2 vinblastine and 100 mg/m^2 cisplatin given every 28 days on days 1 and 8 for the treatment of advanced non-small-cell lung cancer, we noted a high incidence of progressive peripheral neuropathy, which continued for several months after the discontinuation of cisplatin chemotherapy. Of the six patients treated, four received at least three cycles of therapy (median total cisplatin dose, 685 mg/m^2; range, 500–725 mg/m^2). All four patients developed a progressive peripheral neuropathy, with a worsening of toxicity by 1–3 grades over the 2–3 months after cisplatin discontinuation. One patient progressed from grade I (mild paresthesia) to grade IV (inability to ambulate) over a period of 3 months after the discontinuation of therapy. Stricter rules for early dose de-escalation and discontinuation may be required for very high-dose cisplatin regimens. Delayed progressive neuropathy should be recognized as a possible late complication of this form of therapy.

Introduction

Although myelosuppression is the dose-limiting toxicity of many chemotherapeutic agents, the dose-limiting toxicities of cisplatin have included nephrotoxicity, nausea/vomiting, and neurotoxicity [10]. Nausea/vomiting and nephrotoxicity have been ameliorated through the use of potent antiemetics and vigorous hydration. However, there is not yet a generally accepted remedy for cisplatin neurotoxicity.

Cisplatin neurotoxicity principally occurs in the form of ototoxicity or peripheral neuropathy. Peripheral neuropathy after standard-dose cisplatin ($\leq$120 mg/m^2) is characterized as proprioceptive and sensory; it may progress to motor involvement but tends to stabilize or minimally and slowly resolve after the discontinuation of cisplatin [10]. Only rarely has delayed progressive peripheral neuropathy been reported after treatment with standard-dose cisplatin [8].

Over the last several years, regimens including very high-dose cisplatin (total dose, 200 mg/m^2) have been developed to increase dose intensity and achieve greater efficacy [5]. A regimen of 40 mg/m^2 daily $\times$5 led to prohibitive neurotoxicity after a total dose of 600 mg/m^2 [9]. More recently, a regimen involving 100 mg/m^2 given on days 1 and 8 has been introduced and has reported less neurotoxicity [2]. We report our observations of progressive peripheral neuropathy after the cessation of therapy during a pilot study involving a very high-dose cisplatin-based regimen.

Patient selection and treatment

Six patients were treated in a pilot study involving a regimen combining 5 mg/m^2 vinblastine given on days 1 and 8 with 100 mg/m^2 cisplatin given on days 1 and 8 for the treatment of stage 3B and stage 4 non-small-cell lung cancer. The treatment regimen was given on a 28-day cycle, with dose adjustments for toxicity. Cisplatin in hypertonic saline (3%) was infused over 2 h. Four cycles of therapy (maximal cumulative cisplatin dose, 800 mg/m^2) were scheduled to be given.

Toxicity was evaluated on days 1 and 8 of each cycle of chemotherapy and monthly thereafter. Peripheral neuropathy was graded according to the following scale: 0, no peripheral neuropathy; grade I, numbness or tingling of the fingers or toes; grade II, numbness or tingling of the hands or feet; grade III, clumsiness in fine movement; grade IV, difficulty in ambulation.

Results

The six patients (three men and three women) entered in this study had a median age of 63 years (range, 40–70 years) and a median Karnofsky performance status of 80% (range, 70%–80%). Histologies included adenocarcinoma of the lung (four patients), bronchoalveolar carcinoma (one patient), and large-cell carcinoma (one patient) (Table 1). Two patients had stage 3B disease (malignant pleural effusion) and four had stage 4 lung cancer (metastases to adrenal glands, bone, or liver). Four patients had received prior radiation therapy and two had been treated with 13-*cis*-retinoic acid [4]. None of the patients had received prior cytotoxic chemotherapy and none had pre-existing peripheral neuropathy. Two of the six patients re-

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Table 1. Progressive paresthesia after very high-dose cisplatin

Patient number	Age/sex	Karnofsky performance status	Histology	Cycles of chemotherapy delivered	Total dose of vinblastine/cisplatin (mg/m^2)	Neuropathy at completion of chemotherapy (grade)	Maximal neuropathy:	
							Months after chemotherapy	Grade
1	63/M	80	Adenocarcinoma	2	15/400	0	5	I
2	70/M	80	Bronchoalveolar carcinoma	3	20/500	II	3	III
3	65/F	70	Adenocarcinoma	2	21/375	I	0	I
4	67/F	80	Adenocarcinoma	4	21/725	I	3	IV
5	40/F	80	Adenocarcinoma	4	32/675	0	2	II
6	59/M	80	Large-cell carcinoma	4	30/675	II	2	III

ceived only two cycles of chemotherapy, which was discontinued due to nephrotoxicity in one case and progression of disease in the other. Both of these patients developed transient grade I peripheral neuropathy (Table 1).

One patient received three cycles of chemotherapy (discontinued due to nephrotoxicity), for a total cisplatin dose of 500 mg/m^2. Grade II peripheral neuropathy, noted at the completion of chemotherapy, progressed 3 months later to grade III but improved to grade II after 5 additional months. Three patients received all four cycles of chemotherapy, for total cisplatin doses of 675, 675, and 725 mg/m^2. They all developed progressive peripheral neuropathy, which worsened by at least one grade after chemotherapy was discontinued. In one case, a grade I peripheral neuropathy progressed to grade IV over 3 months, resolving only to grade III after 5 addtional months. In another case, a patient with no peripheral neuropathy at the completion of chemotherapy developed grade II neuropathy over the next 3 months (Table 1).

Discussion

Peripheral neuropathy has emerged as a major toxicity of very high-dose cisplatin [5]. Although other neurotoxic agents might contribute to the incidence and severity of neuropathy in multiagent regimens, significant peripheral neuropathy has been seen even in single-agent trials of standard-dose [10] and very high-dose cisplatin [9]. Ozols et al. [9] gave single-agent cisplatin at 40 mg/m^2 daily $\times 5$ with hypertonic saline hydration to 19 patients with refractory ovarian cancer and noted severe peripheral neuropathy in 7 patients (37%). Toxicity of very high-dose cisplatin in a multiagent regimen has been demonstrated by Legha and Dimery [6], who gave eight patients cisplatin at 40 mg/m^2 daily $\times 5$ with 0.5 *N* saline hydration, combined with continuous-infusion 5-fluorouracil at 1,000 mg/m^2 daily $\times 5$; these authors noted severe peripheral neuropathy in five patients (62%).

Our regimen included the vinca alkaloid vinblastine, which is considered to be less neurotoxic than the related compound vincristine. One might speculate that even the lower neurotoxicity of vinblastine could contribute to the overall toxicity of a regimen including very high-dose cisplatin. However, the dose of vinblastine used in our regimen was no higher than that given in vinblastine/standard-dose cisplatin regimens in which neurotoxicity has not been a dose-limiting factor. Mollman et al. [7] retrospectively analyzed the frequency and mean dose of cisplatin at the onset of neuropathy in several cisplatin-containing regimens and found the neurotoxicity of vinblastine/cisplatin to be no different from that of non-vinca-containing regimens.

The majority of regimens involving very high-dose cisplatin have used a 40 mg/m^2 daily $\times 5$ schedule [5]. Our patients received 100 mg/m^2 cisplatin on days 1 and 8 of a 28-day cycle. This schedule, described by Gandara et al. [2], is based on pharmacokinetic data suggesting that with weekly doses, free cisplatin does not accumulate to the extent seen with a 5-day schedule, thereby reducing cisplatin toxicity. Indeed, these authors reported severe peripheral neuropathy in only 1 of 17 patients receiving single-agent, very high-dose cisplatin; 4 additional patients experienced milder neuropathies. Gandara et al. [2] gave the drug infusions over 3 h as compared with the 2-h infusions in the present regimen. However, it is unlikely that this difference in infusion rate and duration is sufficient to explain the lower level of neurotoxicity observed in the former study. Only nine patients in Gandara's study received total cisplatin doses of at least 600 mg/m^2 [2]. The rate of neurotoxicity in patients receiving high total doses of cisplatin may therefore have been underestimated. However, other factors potentially affecting neurotoxicity (including additional chemotherapeutic agents) require additional investigation.

Most reports of very high-dose cisplatin have emphasized the increased incidence and severity of neurotoxicity [5]. Our most disturbing observation was the progressive nature of the peripheral neuropathy, with significant worsening over several months following the cessation of cisplatin therapy. Reports of peripheral neuropathy after standard-dose cisplatin generally suggest stabilization and recovery after the discontinuation of treatment [10]. Progression of peripheral neuropathy for several months after chemotherapy was seen in all of our patients who received three or four cycles of cisplatin. Regimens involving very high-dose cisplatin may be intrinsically more neurotoxic. However, it is also possible that the administration of multiple doses of cisplatin in quick succession does not allow sufficient time for full expression of the neurotoxicity of one dose before the next dose is given. Present/guidelines for de-escalation or discontinuation of cisplatin based on neurotoxicity observed on the day of treatment may therefore not be sufficient for regimens in which cisplatin is given so frequently.

Although neurotoxicity was significant, five of our six patients experienced tumor stabilization or improvement, and we are therefore further pursuing this drug combination. However, our ongoing study of vinblastine/high-

dose cisplatin specifies that an upper limit of three cycles may be given and incorporates stricter criteria for dose de-escalation and treatment discontinuation.

Several strategies for the reduction or prevention of cisplatin neurotoxicity are presently under investigation. The cysteamine derivative WR-2721 may prevent both cisplatin-induced nephrotoxicity [3] and cisplatin-induced neurotoxicity [7]. Mollman et al. [7] noted a statistically significant decrease in the frequency of peripheral neuropathy and a statistically significant increase in the mean dose of cisplatin at the onset of neuropathy when WR-2721 was given with standard-dose cisplatin. Another option would involve use of the cisplatin analogue carboplatin, which appears to have a spectrum of antitumor activity similar to that of cisplatin but a markedly diminished potential for neurotoxicity [1]. Use of these agents may enable the further development of regimens involving very high-dose cisplatin without the severe and progressive neuropathy that is presently the dose-limiting factor.

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