Prolonged Nausea and Vomiting after High Dose Chemotherapy and Autologous Peripheral Stem Cell Transplantation in the Treatment of High Risk Breast Carcinoma

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BACKGROUND. Nausea and vomiting immediately after chemotherapy is a well recognized complication of cancer drug treatment; it is usually short-lived and controllable by modern antiemetics. The authors report a high incidence of prolonged nausea and vomiting after high dose chemotherapy with autologous peripheral stem cell transplantation (PSCT) in the treatment of high risk breast carcinoma patients.

METHODS. Patients with high risk breast carcinoma were conditioned with high dose carmustine, cisplatin, and cyclophosphamide followed by autologous PSCT. In Part I of the study, patients who received PSCT at UCLA Medical Center were identified if they were either readmitted with dehydration secondary to nausea and vomiting or referred to a gastroenterology specialist for the treatment of intractable nausea and vomiting. In Part II of the study, the authors examined a series of 38 women treated at UCLA Medical Center in 1993 for high risk breast carcinoma to determine the incidence of prolonged postchemotherapy nausea and vomiting (PPNV) after PSCT. These women were followed at 2-week intervals with a quality of life evaluation that included questions about nausea and vomiting.

RESULTS. In Part I of the study, the authors identified 9 women with more than 1 month of significant nausea and vomiting after PSCT without evidence of obstruction or mucositis. Hospitalization was frequently required for hydration. Gastroparesis was found in all four patients who underwent gastric emptying studies. The nausea and vomiting responded to the promotility drug cisapride and high dose corticosteroids. In Part II of the study, the authors found that PPNV was frequent; 24% of patients had significant nausea and 18% had significant vomiting 6 weeks after PSCT, despite treatment with standard antiemetics.

CONCLUSIONS. PPNV is a frequent complication of high dose chemotherapy with the aforementioned regimen. It may be due to gastroparesis and represents a form of gastrointestinal toxicity to chemotherapy not previously reported. ***Cancer* 1997;79:1698–702.** © *1997 American Cancer Society.*

KEYWORDS: nausea, vomiting, chemotherapy-induced, breast neoplasms, autologous transplantation, cisplatin, carmustine, cyclophosphamide.

The advent of new methods to support hematopoiesis has allowed the use of higher dose chemotherapy in the treatment of solid tumors. In particular, the use of high dose chemotherapy with autologous stem cell support for the treatment of breast carcinoma has become increasingly common and may offer a survival advantage over standard dose therapy.[1,2] Although most patients tolerate this treatment well, a significant proportion have pulmonary and other toxicities.[3]

Although nausea and vomiting are universal in the first 24 hours after high dose cisplatin without antiemetic therapy,[4] the use of prophylactic combination antiemetic therapy has reduced the incidence of nausea and vomiting in the first 24 hours by greater than two-thirds.[5] Delayed nausea and vomiting, defined as nausea or vomiting beginning more than 24 hours after the initiation of chemotherapy, is particularly common with cisplatin but also can occur with cyclophosphamide.[6] Delayed nausea and vomiting usually peaks within 2 days[7] and is more resistant to current antiemetic therapy than is acute nausea and vomiting.[8–10] In contrast to immediate and delayed nausea and vomiting, we have noted frequent cases of a quite different syndrome of prolonged severe nausea and vomiting lasting up to 2 months after treatment with high dose chemotherapy with autologous stem cell transplantation for breast carcinoma. We define *prolonged* postchemotherapy nausea and vomiting (PPNV) as nausea and vomiting persisting more than 2 weeks after chemotherapy without mucositis or obstruction. PPNV results in significant morbidity in these patients and may represent a more general response to high dose therapy.

We report a series of nine cases of PPNV after a standardized conditioning chemotherapy protocol for autologous peripheral stem cell transplantation (PSCT) in patients with high risk breast carcinoma. We endeavored to define its incidence by examining previously collected quality of life information in a separate group of 38 women undergoing autologous PSCT for treatment of high risk breast carcinoma.

MATERIALS AND METHODS

Part I

Nine patients were identified as having severe nausea and vomiting after treatment with a standardized PSCT protocol for high risk breast carcinoma between September 1994 and March 1996 at UCLA Medical Center. Patients were identified if they were readmitted to UCLA Medical Center after discharge after PSCT with dehydration secondary to nausea and vomiting, or were referred to a gastroenterologist (J.R.H.) for intractable nausea and vomiting. All patients had received a standardized conditioning protocol comprised of carmustine (BCNU), 600 mg/m^2; cisplatin, 55 mg/m/day^2; and cyclophosphamide, 1875 mg/m/day^2. Cyclophosphamide and cisplatin were administered on Days −5 through −3 and BCNU was administered on Day −2 prior to transplantation (Day 0).

Antiemetic medication comprised of prochlorperazine, 10 mg intravenously; lorazepam, 1.0 mg/m^2; and diphenhydramine, 25 mg intravenously, were administered to all patients prior to each dose of chemotherapy. In addition, prochlorperazine, 1.0 mg/m^2/hour, was administered by continuous intravenous infusion for 48 hours whereas lorazepam and diphenhydramine were administered throughout the hospital stay every 4 and 6 hours, respectively, unless not clinically indicated. No antiemetic medication was routinely prescribed after discharge.

Part II

In 1993, as part of another study, a quality of life questionnaire was administered after discharge every 2 weeks for a total of 8 weeks to 38 women receiving PSCT for high risk breast carcinoma. All these women received the same chemotherapy and antiemetic treatment as did the nine women discussed earlier. Several questions pertaining to nausea and vomiting were included in the questionnaire. Specifically, patients were asked to rate their nausea and vomiting on scales from 1 to 4 (1: not at all; 2: a little bit; 3: quite a bit; and 4: very much). Follow-up phone interviews were made when patients failed to return the questionnaires. The response rate to the questionnaires was 92%.

RESULTS

Part I

Table 1 gives the clinical characteristics of nine patients with prolonged nausea and vomiting after autologous PSCT for high risk breast carcinoma. The average age of the patients was 43 years. Three patients had Stage II breast carcinoma, five had Stage III, and one had Stage IV. Seven women received chemotherapy with cyclophosphamide, doxorubicin, and 5-fluorouracil prior to undergoing autologous PSCT, whereas two patients received cyclophosphamide, methotrexate, and 5-fluorouracil. Two of the patients also received paclitaxel. Seven of the nine patients reported nausea and vomiting requiring outpatient antiemetics, including prochlorperazine, lorazepam, metoclopramide, or granisetron, at the time of their initial discharge after PSCT. The remaining two patients developed nausea and vomiting approximately 1–1.5 months after discharge. Five of the patients required hospitalization for hydration or intractable nausea and vomiting at an average of 39 days (range, 11–63 days) after PSCT.

Patients were evaluated for other causes of nausea and vomiting. Mechanical obstruction of the upper gastrointestinal tract was ruled out in all patients by performing a barium upper gastrointestinal series or upper endoscopy. Of the six patients who underwent upper endoscopy, two had mild esophagitis consistent with recurrent emesis whereas the other four patients had normal exams. None of the patients were taking narcotics or other drugs likely to cause nausea and vomiting. Marked delay in the emptying of the stom-

TABLE 1
Prolonged Postchemotherapy Nausea and Vomiting Patient Characteristics

Patient no.	Age (yrs)	Prior chemotherapy	Hospitalizations for N/V (Days after PSCT)	GI procedure(s)	Complications after PSCT
1	50	CAF	11, 19, 28	Normal EGD: delayed gastric emptying,	None
2	49	CAF	61	Mild esophagitis on EGD	Shingles immediately after PSCT
3	44	CAF	None	UGI normal	Pneumonitis responsive to steroids
4	35	CMF, paclitaxel	54	Mild esophagitis on EGD	Recurrence of breast carcinoma
5	43	CAF	None	Normal UGI; delayed gastric emptying	None
6	28	CAF	42	Normal EGD; delayed gastric empyting	Diffuse arthralgias responsive to steroids
7	47	Doxorubicin + CMF	63	Hiatal hernia on EGD	Pneumonitis responsive to steroids/(HUS)/neuropathy
8	50	CAF	None	Normal EGD; delayed gastric emptying	None
9	36	CAF, XRT, paclitaxel	None	Normal UGI	Brain abscess

N/V: nausea/vomiting; PSCT: autologous peripheral stem cell transplantation; GI: gastrointestinal; CAF: cyclophosphamide, doxorubicin, and 5-fluorouracil; EGD: esophagogastroduodenoscopy; UGI: upper gastrointestinal series; CMF: cyclophosphamide, methotrexate; and 5-fluorouracil; HUS: hemolytic uremic syndrome; XRT: radiotherapy.

ach (gastroparesis) was present in all four patients who underwent radionuclide gastric emptying studies.

Due to the clinical impression of gastroparesis and the abnormal gastric emptying studies, all patients were treated with the promotility agent cisapride, 10–20 mg 4 times daily, and had partial resolution of nausea and vomiting. This was often enough to prevent repeat hospitalization. It was also noted that Patient 4 had rapid improvement in her symptoms after treatment with high dose corticosteroids for BCNU pulmonary toxicity. Several subsequent patients responded to high dose steroids in a similar fashion.

Part II

The results of the questionnaire are summarized in Figures 1–3. Figure 1 shows the overall incidence of any nausea or vomiting after autologous PSCT in the treatment of high risk breast carcinoma in 38 consecutive women. From Weeks 2 to 8, the incidence of nausea ranged from 35–60% and the incidence of vomiting from 25–58%. The highest incidence of both prolonged nausea and vomiting occurred between Weeks 2 and 4. A significant proportion of patients had nausea and vomiting at the end of the study.

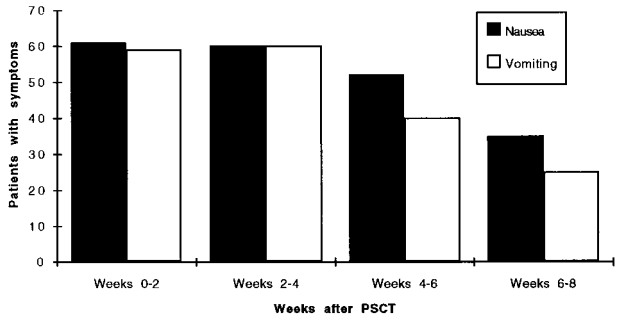

FIGURE 1. The overall incidence of nausea or vomiting in 38 consecutive women after autologous peripheral stem cell transplantation (PSCT) for the treatment of high risk breast carcinoma is shown. The incidence of nausea ranged from 35–60%, whereas the incidence of vomiting ranged from 25%–58%.

The severity of nausea and vomiting as rated by the patients is shown in Figures 2 and 3. The highest incidence of both severe nausea or vomiting (ratings of 3 [quite a bit] or 4 [very much]) occurred between

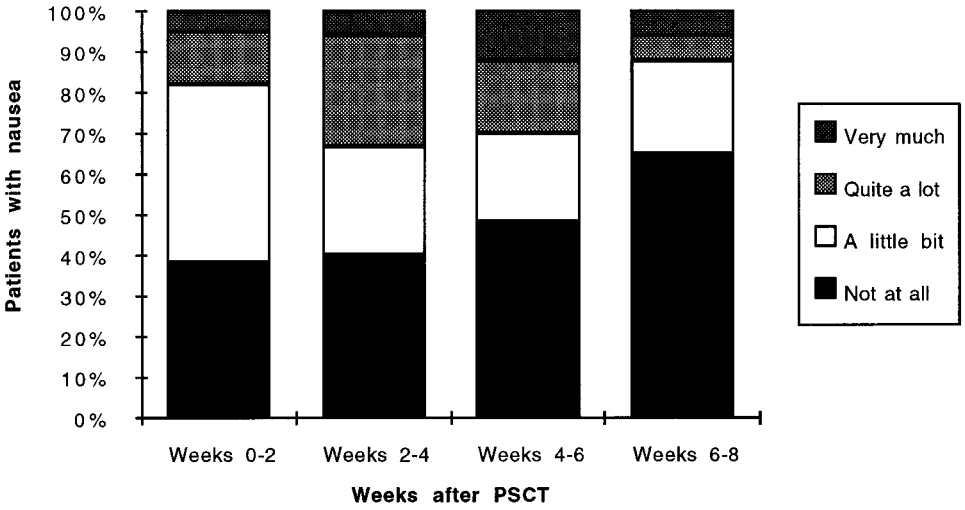

FIGURE 2. The severity of nausea after autologous peripheral stem cell transplantation (PSCT) as rated by the patients is shown. The highest incidence of severe nausea (ratings of 3 [quite a bit] or 4 [very much]) occurred between Weeks 4 and 6.

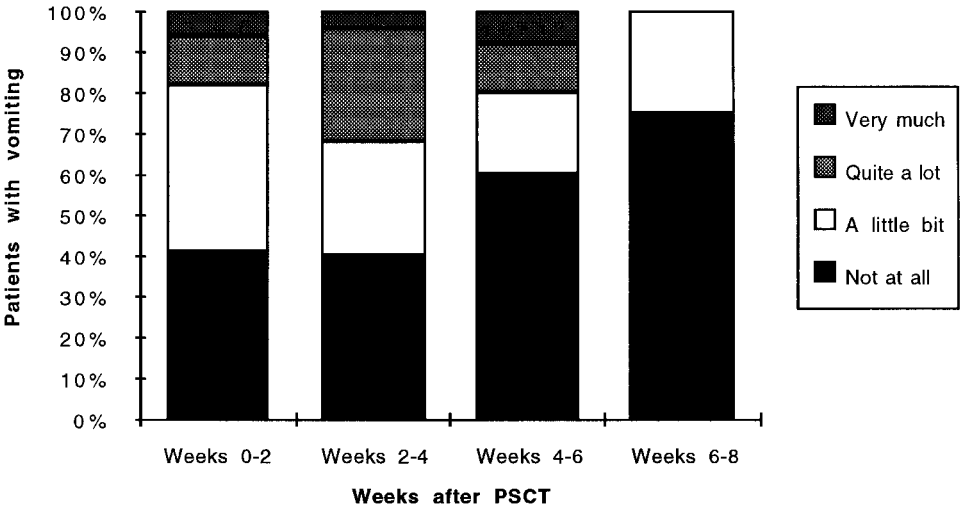

FIGURE 3. The severity of vomiting after autologous peripheral stem cell transplantation (PSCT) as rated by the patients is shown. As with nausea, the highest incidence of severe vomiting (ratings of 3 [quite a bit] or 4 [very much]) occurred between Weeks 4 and 6.

Weeks 4 and 6. Although none of the women experienced severe vomiting between 6 and 8 weeks after PSCT, 12% of women continued to experience severe nausea between 6 and 8 weeks after PSCT.

DISCUSSION

To our knowledge, this is the first report of a syndrome of prolonged nausea and vomiting after high dose chemotherapy. No similar cases were found in a search of MEDLARS from 1969 to 1996. PPNV is a relatively frequent complication resulting in significant morbidity in the growing number of patients undergoing high dose chemotherapy with autologous PSCT in the treatment for breast carcinoma.

Unlike most chemotherapy-induced nausea and vomiting, PPNV lasts for weeks to months and is unresponsive to routine antiemetic therapies. Gastroparesis appears to play an important part in the syndrome because symptoms are consistent with delayed gastric emptying and all patients who underwent radionucleotide gastric emptying studies had significantly abnormal results. Furthermore, treatment with cisapride, a

promotility agent, ameliorated symptoms. Although not life-threatening, the symptoms have a severe negative impact on the patient's quality of life and frequently increase costs by resulting in repeat hospitalization for dehydration. Fortunately, the syndrome appears to be self-limited and most patients improve with treatment and time.

The mechanism of PPNV remains obscure. Most likely it is due to a chemotherapy-induced neuropathic gastroparesis. Up to 20% of patients receiving cisplatin therapy may develop peripheral neuropathy, although this depends on the dose of cisplatin and concomitant chemotherapy.[11] A case of prolonged gastroparesis after cisplatin therapy has been reported, although other neurotoxic drugs also had been administered.[12]

Other possible mechanisms include BCNU or cyclophosphamide toxicity. Although these agents may cause acute or delayed nausea and vomiting, they are not noted to be neurotoxic. However, several of the patients in the current study had evidence of BCNU toxicity at other sites. The rapid response to high dose corticosteroids also is reminiscent of that observed in the treatment of BCNU pulmonary toxicity.[13]

PPNV may represent a common gastroparetic response to various chemotherapeutic regimens. Multiple cycles of chemotherapy may obscure PPNV as patients receive additional nausea-inducing agents. However, high dose chemotherapy with autologous PSCT offers an ideal model to study PPNV because patients do not receive any further chemotherapy after the initial treatment. With the increasing number of autologous PSCT with high dose chemotherapeutic agents being used for the treatment of breast carcinoma, the accompanying PPNV may result in significant morbidity and additional cost in a large number of patients. We suggest further study of the syndrome, including radionucleotide gastric emptying studies before and after chemotherapy, which may reveal subsets of patients more likely to develop PPNV and patients with less symptomatic delayed emptying. We also suggest a rigorous comparison of cisapride and corticosteroid therapy in symptomatic patients.

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