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REVIEW ARTICLE

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Antiemetic therapy for multiple-day chemotherapy and high-dose chemotherapy with stem cell transplant: review and consensus statement

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Abstract The objective of this paper is to evaluate the efficacy of modern antiemetic therapy for chemotherapy-induced nausea and vomiting for patients receiving multiple-day or high-dose chemotherapy. Published phase II and phase III studies as well as their personal experiences were evaluated by the authors to develop this consensus statement. The largest published experience with multiple-day chemotherapy is with 5-day cisplatin combination chemotherapy. The introduction of 5-HT3 antagonists greatly improved emetic control. However, day 4–5 nausea as well as delayed nausea and vomiting remains a clinical problem despite the inclusion of dexamethasone. A 5-HT3 antagonist plus dexamethasone is the preferred current option for patients receiving high-dose chemotherapy with stem cell transplant. However, the results do not appear as successful as for highly emetic standard-dose chemotherapy.

Keywords 5-HT3 antagonist · Multiple-day chemotherapy · Antiemetics · High-dose chemotherapy

Introduction

During the past 15 years, there have been major advances in the management of chemotherapy-induced nausea and vomiting (CINV). The introduction of ondansetron, the first 5-HT3 antagonist for CINV, was a milestone in antiemetic therapy. Subsequently, the inclusion of dexamethasone further improved results for patients receiving highly and moderately emetogenic agents. Despite improvements in acute nausea and vomiting, delayed CINV remained a problem, representing a separate mechanism. However, poor control of acute nausea and vomiting was a factor in delayed nausea and vomiting.

Most of the published experience has been with single-day highly emetic agents, such as cisplatin, or an anthracycline plus cyclophosphamide. There is less infor-

mation about the optimal strategy for multiple-day chemotherapy, such as cisplatin combination chemotherapy in germ cell tumor patients. High-dose chemotherapy with stem cell transplantation is another area of controversy for CINV. These are complicated cases with multiple factors potentially causing nausea and vomiting and treated with eclectic high-dose chemotherapy regimens. The purpose of this paper is to provide a consensus statement derived from published articles as well as personal experience of the authors about antiemetic therapy for multiple-day and high-dose chemotherapy with stem cell transplant patients.

Multiple-day chemotherapy

Most patients receiving multiple-day cisplatin have testicular cancer. The standard treatment with testicular cancer, bleomycin+etoposide+cisplatin (BEP) utilizes cisplatin in a dosage of 20 mg/M^2 for 5 consecutive days every 3 weeks for 3 or 4 courses. In the past, multiple-day cisplatin was occasionally used in some studies for small cell lung cancer as well. This is rarely done today, however.

Prior to the advent of successful antiemetics, patients receiving 5-day courses of cisplatin had the most severe nausea and vomiting on the first day, with a lessening of the emetic effect of cisplatin with succeeding days of treatment. The average testicular cancer patient would have 10 emetic episodes on the first day of chemotherapy with five, four, three, and three emetic episodes on days 2–5 respectively (10). This trend has reversed with modern antiemetic regimens that include a 5-HT3 antagonist+dexamethasone; the first 2 days usually have complete emetic control, but days 3–5 now have the worst nausea and even some vomiting.

In 1979, Indiana University and the University of Arizona published a study evaluating a phenothiazine, prochlorperazine, compared to a THC derivative, nabilone. In this study, 2 mg. of nabilone was compared to 10 mg. of prochlorperazine every 6 h starting 30 min before chemotherapy. This was a phase III double-blinded study that was done independently at Indiana University (70 patients receiving cisplatin+vinblastine+bleomycin) [PVB] and 43 patients treated at Arizona, mainly with lymphoma. There was a crossover design, and a visual analog scale was used for nausea. A complete remission (CR) was defined as no nausea and vomiting, and a partial remission was defined as >50% decrease in the duration or severity of nausea and emetic episodes with the crossover design. The CR rate was 8% for nabilone versus zero with prochlorperazine. There were no CRs in the PVB population. There was a 72% partial remission rate for nabilone compared to 36% for prochlorperazine, and furthermore, on an open-label design after the two courses of therapy, 75% of the patients chose nabilone compared to only 15% prochlorperazine [10]. Metoclopramide was later successfully used for cisplatin-induced nausea and vomiting. However, the testicular cancer patient population is a young group, and they are more prone to the extrapyramidal side effects of this effective agent.

Subsequent studies with multiple-day cisplatin were performed with the first 5-HT3 antagonist, ondansetron. At Indiana University, a phase II study was conducted in 35 patients receiving 4–5 days of cisplatin combination chemotherapy, including 24 chemo-naïve patients [8]. Ondansetron was given in a dosage of 0.15 mg/kg ×3 intravenously on each day of cisplatin. Ten patients (29%) had no vomiting, and 18 (51%) had two or fewer emetic episodes during the entire 4–5 day course. The best CR result (77%) was seen on day 1. As mentioned above, this was in marked contrast to results prior to the 5-HT3 era, documenting the fact that day-1 cisplatin now had the best antiemetic results in these multiple-day platinum regimens.

At Indiana University, a subsequent phase III, double-blind comparison of intravenous ondansetron versus metoclopramide for patients receiving multiple-day, cisplatin-based chemotherapy was performed [14]. Forty-five patients were entered utilizing ondansetron versus 1 mg/kg ×3 metoclopramide. Thirty percent had no emetic episodes with ondansetron compared to 9% with metoclopramide, and again, the best results were seen on day 1 (78% no emesis with ondansetron versus 14% for metoclopramide). Greater than five emetic episodes were seen in 50% of the metoclopramide patients compared to 9% with ondansetron, and there were also extrapyramidal side effects in 13 of the metoclopramide patients in this young patient population. Although this was a small phase III study, it provided evidence for the superiority of ondansetron compared to metoclopramide for patients receiving multiple-day chemotherapy.

Investigators at Indiana University performed a randomized study of ondansetron versus ondansetron+dexamethasone+chlorpromazine [9]. It is doubtful that the chlorpromazine contributed. Forty-four patients were randomized to ondansetron+/-dexamethasone 8 mg. before and 4 mg 4 and 8 h after the first 2 days of cisplatin, together with chlorpromazine 50 mg every 4 h each day of cisplatin. Nineteen of 22 (86%) versus ten of 22 (46%) had fewer than three emetic episodes throughout the course of treatment, and 55% versus 32% had no emetic episodes. The median visual analog score for nausea was 15 for ondansetron versus 5.5 for the combination. This established the value of adding dexamethasone in this patient population.

Dexamethasone could cause potential side effects if given for all 5 days of cisplatin. Therefore, dexamethasone was given only on days 1 and 2 as historically, before ondansetron, those were the worst emetic days. This was also before there was a full understanding of delayed nausea and vomiting from cisplatin. A subsequent phase

Table 1 Emesis with multiple-day cisplatin chemotherapy. Median day 1. *Ond* ondansetron, *Gran* granisetron, *Dex* dexamethasone, [a]*CR* (complete remission) no emetic episodes day 1, [b]*CR* no emetic episodes days 1–5 cisplatin, [c]*PR* (partial remission) 0–2 emetic episodes days 1–5 cisplatin

Reference	No. Patients	Agent	Emesis (CR)[a]	CR[b]	CR/PR[c]
[1]	35	Prochlorperazine	10 (0%)	0	–
[2]	35	Ond	0 (77%)	29%	51%
[3]	23	Ond	0 (78%)	30%	–
[4]	22	Ond	0 (82%)	32%	46%
[7]	359	Ond or gran	0 (90%)	42%	–
[4]	22	Ond+dex	0 (95%)	55%	86%
[5]	47	Ond+dex	Unknown	55%	66%
[6]	24	Ond+dex	0 (100%)	58%	71%

III study compared the same dose of ondansetron with the variable being dexamethasone on days 1 and 2 versus dexamethasone on days 4 and 5, and there was no difference in nausea or vomiting.

Dr. Lothar Weissbach published a letter to the editor in Lancet for the multi-day cisplatin emesis study group. Ondansetron 32 mg IV plus dexamethasone 20 mg was compared in a double-blind, randomized study to metoclopramide plus dexamethasone. Analysis was made after 95 patients entered. Complete or major control of emesis was achieved in 66% of ondansetron versus 27% of metoclopramide patients (p=0.00016). There was complete control of emesis in 55% versus 19% [16]. Dexamethasone was given with each day of cisplatin.

Baltzer and colleagues at Memorial Sloan-Kettering evaluated ondansetron 0.3 mg/kg IV given 30 min before and 3.5 h after cisplatin plus dexamethasone 20 mg IV 15 min pre-cisplatin daily. Of 24 evaluable patients, no emesis was seen in 100%, 88%, 67%, 67%, and 73% on days 1–5, and 58% reported no emesis throughout their 5-day course of cisplatin. However, 25%, 27%, and 29% had three or more emetic episodes on days 3–5 [4]. Again, dexamethasone was utilized each day of cisplatin.

A large European study was conducted randomizing patients receiving 5-day cisplatin to granisetron versus ondansetron [11]. Three hundred fifty-nine patients were randomized. Sixty had testicular cancer, 91 had head and neck cancer, and 65 had lung cancer as the three most prevalent tumor types. Granisetron was given as a single, 3 mg, intravenous dose versus ondansetron 24 mg intravenously. The 5-day complete remission rate was 44% for granisetron versus 40% for ondansetron. As was true with other similar studies, there was little, if any, difference between these two 5-HT3 antagonists.

At the present time, patients receiving 5-day courses of cisplatin for testicular cancer will have little or no nausea or vomiting during the first 3 days of chemotherapy. The worst nausea is seen on days 4 and 5, as well as on days 6, 7, and 8. Whether this all reflects delayed nausea from the first day, which historically had been the most severe day, or whether there are other mechanisms involved is not clear at the present time. Similar strategies for delayed nausea and vomiting for multiple-day cisplatin courses should be utilized similarly to single-day high dose cisplatin. The current recommendation is to employ oral dexamethasone as a single 20 mg dose on days 1 and 2, dexamethasone 8 mg p.o. bid on days 6 and 7, and 4 mg bid on day 8. Neither palonosetron nor aprepitant has been studied in this patient population. Overall results are depicted in Table 1. With single-agent 5-HT3, 77–82% have complete protection on day 1 and 29–42% CR throughout the 5-day course. The addition of dexamethasone improves the day 1 CR rate to 95–100% and 55–58% for 5-day cisplatin treatment. It is unknown whether there is added benefit from daily dexamethasone during the 5-day cisplatin courses.

Guidelines

Patients receiving multiple-day cisplatin should receive a 5-HT3 antagonist plus dexamethasone for acute nausea and vomiting and dexamethasone for delayed nausea and vomiting. The Multinational Association of Supportive Care in Cancer (MASCC) level of confidence: high; level of consensus high. The American Society of Clinical Oncology (ASCO) level of evidence: 2; grade of recommendation: A.

Refractory emesis and rescue antiemetics

The major value of antiemetics is to prevent nausea and vomiting. Once a patient is actively vomiting from chemotherapy, the results of our effective antiemetics are modest, at best. When a patient is having persistent nausea and vomiting, it is also important to make certain that the cause is from the chemotherapy rather than other factors such as hypercalcemia, azotemia, brain metastases, gastric outlet obstruction, or narcotic analgesics. Dr. Aapro recently published an excellent paper concerning this topic [1]. As pointed out in that paper, a very common cause for refractory emesis is inadequate initial treatment.

There are no level 1 or level 2 evidence-based guidelines for what to do in this situation. Different approaches have been utilized, such as switching to a different 5-HT3 [7] or adding other agents, such as dopamine antagonists or benzodiazepines or neuroleptic agents, such as phenothiazines. Palonosetron is a new 5-HT3 agent, and

whether the substitution of this would be beneficial is unknown. Likewise, the same is true for the NK-1 antagonist aprepitant. Novel agents, such as olanzapine, could also be considered [12]. Olanzapine has action in multiple dopaminergic, serotonergic, muscarinic, and histaminic receptor sites.

High-dose chemotherapy

There is very little data on the effective use of modern antiemetics for patients getting high-dose chemotherapy on a bone marrow transplant unit. Most are phase II studies of a 5-HT3 antagonist alone or combined with dexamethasone. One of the major problems is that the nausea and vomiting is due to multiple causes, including prophylactic antibiotics, narcotic analgesics that are used for mucositis, as well as the chemotherapy-induced nausea and vomiting. In addition, the use of total-body irradiation can be a confounding factor. Cross-comparison of studies is difficult due to the varied regimens and different patient populations.

Vinet, et al. published the first study of a 5-HT3 antagonist in patients receiving high-dose chemotherapy and stem cell transplant. Thirty-three patients with malignant melanoma were treated with melphalan in dosages of 140–200 mg/M^2 intravenously. Patients on ondansetron had a 15% complete remission rate, and another 27% had two or less emetic episodes [15].

Perez, et al. evaluated single-agent ondansetron in 24 patients receiving high-dose chemotherapy. Only a single patient achieved a CR [13]. That paper also provides a good review of antiemetic studies published before 1999 in patients receiving high-dose chemotherapy.

Climent, et al. evaluated granisetron, dexamethasone, haloperidol, and lorazepam in breast cancer patients receiving high-dose cyclophosphamide, thio-tepa, and carboplatin. Only 30% (nine of 30) obtained complete or major protection during the 4-day course, with best results on days 1–2 [6]. By contrast, Abbott, et al., at M.D. Anderson, utilized granisetron plus dexamethasone in 26 patients treated with high-dose cyclophosphamide and total-body irradiation, and 50% had CR and 48% had major responses [2]. Tropisetron has also been used with dexamethasone in 31 stem cell transplant patients. Complete or major protection ranged from 71% to 83%, again with best results on day 1 of the chemotherapy regimen [5].

Table 2 5-HT3 agents for high-dose chemotherapy. *Ond* ondansetron, *CR* complete remission, *PR* partial remission, *Gran* granisetron, *Dex* dexamethasone,*Trop* tropisetron

Reference	No. Patients	Treatment	CR	CR/PR
[11]	33	Ond	15%	42%
[12]	24	Ond	4%	–
[13]	30	Gran+dex	–	30%
[14]	26	Gran+dex	50%	98%
[15]	31	Trop+dex	–	75%
[16]	82	5-HT3+dex	20%	–

Ballen, et al. published the largest phase II experiences. Eighty-two patients receiving high-dose chemotherapy with allogenic or autologous stem cell transplant at the University of Massachusetts between 1997 and 2000 were evaluated. Emetic episodes were recorded, and nausea was categorized as none, mild, moderate, or severe. A 7-day questionnaire was used to capture this information. Antiemetic treatment was a 5-HT3 antagonist+/-dexamethasone. Only four patients (5%) reported no nausea. The nausea was worse on day 5, with 83% reporting some nausea. Sixteen patients (20%) reported no emesis. Once again, results were worse on day 5, with 36 patients (44%) experiencing emesis [3]. Results from these six studies are depicted in Table 2. With the exception of reference number 13, the CR rate ranged from only 4 to 20%.

In summary, it is apparent that control of nausea and vomiting with high-dose chemotherapy and stem cell transplant remains a challenge. Standard therapy appears to be a 5-HT3 with dexamethasone. However, the results are less impressive than for standard-dose highly emetic chemotherapy. Neither palonosetron nor aprepitant has been studied in this patient population.

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