Impact of aprepitant on emesis control, dose intensity, and recurrence-free survival in a population-based cohort of head and neck cancer patients receiving high-dose cisplatin chemotherapy

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Background Standard care for locally advanced head and neck cancer (HNC) patients consists of high-dose cisplatin with radiation to prolong recurrence-free survival (RFS). However, poorly controlled emesis can compromise optimal dose intensity (DI) and affect disease control.

Objective To evaluate the impact of aprepitant on emesis control, DI, and RFS.

Methods HNC patients treated at the British Columbia Cancer Agency were analyzed. Kaplan-Meier method and adjusted Cox proportional hazard models were used to evaluate RFS in aprepitant users. To control for selection bias, a propensity score analysis was conducted.

Results A total of 192 HNC patients were included: 141 received aprepitant prophylaxis. The aprepitant-treated and untreated groups were comparable in mean age (56.3 vs 58.1 years), male gender (82.3% vs 86.3%), tumor location, and number of metastatic sites. However, more patients in the aprepitant group than in the untreated group had surgically resectable disease (31.2% vs 15.7%, respectively) and better performance status (ECOG 0/1, 87.9% vs 76.4%). Less emesis was reported in the aprepitant group (21.3% vs 28.0%). Patients in the treated group were also more likely to complete 3 cycles of high-dose cisplatin (OR, 2.3; $P = .03$). The propensity score adjusted Cox regression analysis suggested a reduced risk of disease recurrence in patients who received aprepitant (HR, 0.47; 95% CI, 0.17-1.28).

Limitations Potential confounders such as other diseases or treatments that may have influenced the presence of nausea/emesis symptoms.

Conclusion Aprepitant contributed to improved emesis control, enhanced DI, and better adherence to cisplatin chemotherapy.

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Head and neck cancers (HNCs) represent one of the 10 most common cancers worldwide. [1] They comprise a heterogeneous group of malignancies and anatomical sites, with about 90% of HNCs characterized by squamous cell histology.[2] Concurrent chemotherapy with radiation has largely replaced surgery as the main treatment modality because the latter is associated with significant morbidity, including the risk of physical disfigurement and postoperative complications.[3] Despite aggressive treatment, however, prognosis for HNCs remains poor.[3-5] Standard of care for locally advanced HNCs typically consists of 3 cycles of high-dose cisplatin (>70 mg/m2) delivered concomitantly with radiation.[6-9] This regimen has been shown by the Radiation Therapy Oncology Group and in studies by other investigators to confer a significant recurrence-free survival (RFS) benefit.[10] However, platinum-associated toxicities such as renal dysfunction (2%-5% of patients), neuropathy (about 5%), and mucositis (41%-85%) are frequently difficult to manage.[10] In addition, cisplatin can contribute to a number of other physical and nonphysical symptoms including fatigue, irritability, loss of appetite, constipation, aches and pains, weight loss, and a detrimental impact on family and relationships.[11] One of the most debilitating adverse effects is chemotherapy-induced nausea and vomiting (CINV), which occurs in >90% of HNC patients receiving high-dose cisplatin.[7,8,12,13] Severe

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emesis after chemotherapy is a significant predictor of poor adherence to treatment.[14]

CINV can be categorized as acute (within ≤24 hours after chemotherapy) or delayed (>24 hours after chemotherapy).[15] This classification schema is based on temporal differences as well as unique molecular mechanisms that are mediated by serotonin in the peripheral nervous system in the acute phase and substance P within the central nervous system (CNS) in the delayed phase.[16-18] Until recently, antiemetic regimens for acute and delayed CINV consisted of the combination of a 5-HT_3 receptor antagonist (ie, ondansetron) and a corticosteroid (ie, dexamethasone). Although this approach antagonizes serotonin binding at the 5-HT_3 receptors, it does not substantially influence substance P binding at the NK_1 receptors.[16] Therefore, most patients (about 60%-80%) who receive high-dose cisplatin still experience significant emesis during the delayed phase.[16,19] The NK_1 receptor antagonist aprepitant was approved by the US Food and Drug Administration in 2003 for the treatment of chemotherapy-related nausea.[20] The addition of this agent to the standard antiemetic regimen of ondansetron and dexamethasone has been shown in a number of studies to provide significantly better control of emesis after high-dose cisplatin.[21-23] Control of CINV through the addition of aprepitant has also been associated with minimal impact on daily life for treated patients compared with patients who are on conventional therapy.[22] These findings are supported by evidence-based guidelines for the prevention of CINV published by the Multinational Association of Supportive Care in Cancer (MASCC) and the European Society of Medical Oncology (ESMO), both of which support the prophylactic use of aprepitant for the control of CINV in highly emetogenic chemotherapy.[24] Despite the quality of evidence about aprepitant, guideline-concordant practices may not always be followed.[25,26] To date, real world practice patterns of the use of aprepitant in highly emetogenic chemotherapy are rarely described.

In this observational study, data were collected from patients who were receiving high-dose cisplatin chemotherapy for HNC. Specifically, we examined the association between aprepitant use and the incidence of CINV in routine clinical practice. In addition, we explored whether aprepitant use was a valid predictor of completion of all planned cycles of cisplatin as well as clinical outcomes. Findings from this study will provide insight into optimizing the CINV management of HNC patients in the non-trial setting.

Methods

Characteristics of the study setting

The British Columbia Cancer Agency (BCCA) is a provincial-based cancer control program that is responsible for funding and providing cancer treatment to about 4.5 million residents in British Columbia, Canada. The agency is comprised of 5 comprehensive, regional cancer centers that are distributed across different catchment areas of the province so that care can be distributed as equitably as possible to a geographically dispersed population. All of the centers offer a full range of quality cancer services and programs, including ambulatory oncology clinics, chemotherapy suites, radiation facilities, surgical services, inpatient units, palliative care, and the opportunity to participate in major oncology clinical trials for the estimated 15,000-20,000 new patients who are referred to the BCCA annually.

Description of the patient cohort

The analysis included all adult patients aged 18 years or older diagnosed with HNCs during January 2008 to June 2011, who were referred to any one of 5 regional cancer centers of the BCCA for management, and who underwent dual modality treatment with chemoradiotherapy that consisted of 3 planned cycles of high-dose cisplatin (100 mg/m^2). Patients were excluded if they did not receive any cisplatin as part of their chemotherapy regimen or if they had unspecified CINV management. The study time period was chosen to allow for sufficient sample size, adequate follow-up, and reliable ascertainment of data regarding recurrence, progression, and death.

Definitions of covariates and outcomes

For each eligible individual, baseline patient and disease characteristics were abstracted from medical records, such as age, gender, weight, Eastern Cooperative Oncology Group (ECOG) performance status, as well as tumor location, grade, and stage. Additional information that included history of smoking and alcohol use, presence of comorbidities (defined by the presence or absence of specific organ dysfunction or impairments) were ascertained. Details pertaining to treatment and side effects, such as initial cisplatin dose, number of chemotherapy cycles completed, use of aprepitant, and symptoms of nausea and vomiting were also collected.

We defined aprepitant use as a documented prescription and receipt of aprepitant before the first cycle of cisplatin. Delivery of aprepitant after the onset of CINV symptoms or during subsequent chemotherapy cycles was considered a rescue maneuver and not a pre-emptive approach to CINV control. Although rescue might be clinically appropriate in certain circumstances, our definition of aprepitant use is based on the MASCC and ESMO guidelines, which recommend that aprepitant be offered prophylactically in the setting of highly emetogenic chemotherapy. Because the use of 5-HT_3 receptor antagonists and corticosteroids is the standard provincial practice at the BCCA and prescriptions for these antiemetic agents are part of the actual chemotherapy protocol for high-dose cisplatin, we made

the assumption that all patients received these 2 classes of antiemetic medications. Patients who were treated with only ondansentron and dexamethasone formed the control group. For the purposes of this study, any indication of nausea or vomiting constituted an emesis event, which was categorized in a binary fashion (Yes or No) for all of the analyses. It was beyond the scope of this study to reliably capture the severity of nausea or vomiting in the patients because the data were collected retrospectively.

The primary study endpoint was recurrence-free survival (RFS), defined as the time interval from the date of HNC cancer diagnosis to the date of first tumor recurrence (local, regional, or distant); disease progression; or death from any cause. RFS was selected as the main outcome measure because one of the rationales and benefits of concurrent chemoradiotherapy is its potential role in providing disease control. Secondary endpoints included overall survival (OS), defined as the time between the date of HNC diagnosis and death from any cause as well as the rate of completion of 3 full cycles of high-dose cisplatin. At the BCCA, the standard chemotherapy regimen for locally advanced HNCs consists of cisplatin at a dose of 100 mg/m^2, which is to be delivered at weeks 1, 4, and 7 with concomitant radiation.

Statistical analyses

Data were summarized with descriptive statistics, using means, medians, or proportions. Because this study was observational in design, formal sample size and power calculations were not undertaken. Therefore, findings are mainly presented as point estimates and corresponding 95% confidence intervals (95% CIs). To minimize selection bias, a propensity score analysis was conducted to supplement conventional multivariate techniques.[27] Any baseline covariate with a marginal association ($P < .25$) was considered in the propensity score model. A main-effects binary logistic regression model was subsequently developed using variables identified in the previous step, and retained following a backwards elimination process with $P < .10$ designated as the cutoff value to generate final propensity scores. To finely adjust for potential selection bias, the propensity scores were then incorporated as a weighting variable in a Cox proportional hazard regression analysis on RFS and OS, and prognostic factors were retained using a similar backwards elimination procedure but with $P < .05$ specified as the threshold value. All statistical analyses were performed using Stata Version 11.0 (Stata Corp, College Station, TX).

Results

Of 192 eligible HNC patients who were reviewed, 141 (73.4%) received prophylactic aprepitant and 51 (27.6%) did not receive it as part of their first-line antiemetic regimen during high-dose cisplatin chemotherapy. Several imbalances in baseline characteristics were observed between the 2 groups. Specifically, patients treated with aprepitant were less inclined than were those who were not treated preemptively to report a history of smoking (67.1% vs 88.2%, respectively) and alcohol consumption (57.9% vs 78.0%). The treated patients' performance status was also better (ECOG 0/1, 87.9% vs 76.4%) and they were more likely to have had surgery as part of their overall cancer management (31.2% vs 15.7%). Otherwise, patients were comparable with respect to mean age (56.3 vs 58.1 years), weight (78.4 vs 79.8 kg), male gender (82.3% vs 86.3%), tumor location, and number of metastatic sites (median 1 in both groups). Additional details regarding baseline characteristics are summarized in Table 1.

The unadjusted clinical outcomes are highlighted in Table 2. Patients in the aprepitant group tended to experience less vomiting than did those in the control group (21.3% vs 28.0%; odds ratio [OR], 0.69; 95% CI, 0.32-1.28). However, there did not appear to be any notable differences in the development of nausea (76.6% vs 72.0%; OR, 1.27; 95% CI 0.56-2.77). Similarly, the unadjusted rates for RFS and OS were comparable irrespective of receipt of aprepitant (recurrence rate 17.7% vs 19.6% and death rate 17.7% vs 21.6% for the aprepitant and no aprepitant groups, respectively). In contrast, the propensity score weighted logistic regression analysis exploring the completion of 3 full cycles of high-dose cisplatin as an outcome revealed that patients in the aprepitant group were twice as likely as those not treated with aprepitant to have received maximal dose intensity (OR, 2.3; 95% CI, 1.08-5.10; Table 3).

In a separate propensity score adjusted Cox regression analysis with RFS as the endpoint, we observed a strong trend for a reduced risk for disease recurrence (hazard ratio [HR], 0.47; 95% CI, 0.17-1.28) in patients who received aprepitant, as supported by the low point estimate. As illustrated in Table 4, there was also an association between weight before the start of chemotherapy and the risk of recurrence whereby individuals with an elevated initial weight were less likely to recur (HR, 0.98; 95% CI, 0.96-1.00). Conversely, patients with regional or local metastases and those who underwent surgical resection had an increased likelihood of experiencing recurrent cancer.

A propensity score adjusted Cox regression analysis on OS demonstrated that there were no differences in outcomes between the aprepitant group and the control group (Table 5). However, there were other prognostic factors that correlated with OS. Similar to the relationship seen with recurrence, patients with a higher baseline weight were at a reduced risk of death (HR, 0.96; 95% CI, 0.94-0.99). Patients who reported regular alcohol consumption, manifested with regional metastases, suffered a poor per-

formance status, and those whose primary originated in the tongue had a significantly higher risk of death.

Discussion

The current study represents a population-based analysis that explores the real world uptake of aprepitant in patients who underwent highly emetogenic cisplatin-based chemotherapy and radiation for locally advanced HNC. Most of the patients in this cohort seemed to have received appropriate CINV management, but there is room for improvement given that more than a quarter of individuals failed to receive aprepitant as part of their antiemetic regimen before their first cycle of high-dose cisplatin. This practice pattern contrasts the current recommendations from the MASCC and ESMO regarding optimal CINV control and reasons for such contrasts remain.[28] Of note is that there was a reduction in the rate of vomiting in patients who received pre-emptive treatment with aprepitant. More important, aprepitant use was correlated with an increased likelihood of completing 3 full cycles of high-dose cisplatin as well as a trend toward a decreased risk of cancer recurrence.

Because it is uncertain whether the 2 patient populations (aprepitant vs no aprepitant) were inherently different, the finding that aprepitant resulted in potentially fewer cancer recurrences cannot be confirmed. However, the reported trend might suggest that patients managed with prophylactic aprepitant were more successful in adhering to their planned chemotherapy. In fact, improved emesis control has been shown to result in improved tolerance and a higher dose-delivery of cisplatin.[29] This is not surprising because patients with well controlled side effects, particularly CINV, are often in better positions physically and psychologically to continue with subsequent treatment cycles at optimal doses. Smit and colleagues have reported on lung cancer patients who stopped cisplatin-based chemotherapy because of severe emesis.[30] Those same patients were also hospitalized more frequently and for longer durations than those who did not experience CINV.[30] It has been suggested that the risk of debilitating emesis is highest in the early courses of chemotherapy (ie, first several cycles).[31] Given that cisplatin for HNCs is administered at very high doses (100 mg/m^2) and usually only for 3 cycles during radiation, the consequences of poor CINV control on outcomes during this short treatment time window can be particularly significant. It is important to note that aprepitant and chemotherapy dose intensity seem to pose a more pronounced impact on RFS than on OS. This is consistent with findings in other studies showing that the major benefit of chemoradiotherapy in HNCs is its locoregional instead of distant disease control.

TABLE 1 Baseline patient and treatment characteristics

Characteristic	Received aprepitant (n = 141)	Did not receive aprepitant (n = 51)
Age, y (mean SD)	56.3 (8.4)	58.1 (7.2)
Weight, kg (mean SD)	78.4 (19.4)	79.8 (17.4)
Gender, n (%)		
Male	116 (82.3)	44 (86.3)
Female	25 (17.7)	7 (13.7)
Risk factors		
≥1 comorbidity present	107 (75.9)	43 (84.3)
Positive smoking history	95 (67.1)	45 (88.2)
Current alcohol drinker	82 (57.9)	40 (78.0)
Surgically treated	44 (31.2)	8 (15.7)
ECOG status		
0	43 (30.5)	12 (23.5)
1	81 (57.4)	27 (52.9)
≥2	10 (7.1)	9 (17.6)
Missing	7 (5.0)	3 (5.4)
Tumour location, n (%)		
Tongue	53 (37.6)	17 (33.3)
Mouth	13 (9.2)	2 (3.9)
Tonsil	47 (33.3)	11 (21.6)
Larynx	14 (9.9)	7 (13.7)
Other	14 (9.9)	14 (27.4)
Locoregional metastatic sites		
Median no. (range)	1 (0-3)	1 (0-4)
Lung	6 (4.3)	2 (3.9)
Lymph nodes	127 (90.1)	46 (90.0)
Cisplatin therapy		
Starting dose (mg/m^2)[a]	182.6	157.6
Cycles, median no. (range)[b]	3 (1-3)	3 (1-3)
Completion of 3 cycles, n (%)[c]	96 (68.1)	27 (52.9)

ECOG, Eastern Cooperative Oncology Group

[a]P = .015. [b]P = .47. [c]P = .053.

It should be noted, however, that such findings require confirmation from randomized controlled trials.

Aprepitant use was associated with a numerical reduction in rates of vomiting, although this was not statistically significant. The imbalances in baseline patient characteristics coupled with the small sample size may explain why the difference in rates of emesis between the aprepitant and control groups was less drastic than expected. Previous studies have consistently shown that there are a number of

TABLE 2 Clinical outcomes

Outcome, n (%)	Received aprepitant (n = 141)	Did not receive aprepitant (n = 51)
CINV outcomes[a]		
Any vomiting	30 (21.3)	14 (28.0)
Any nausea	108 (76.6)	37 (72.0)
Disease recurrence[b]		
Relapsed	25 (17.7)	10 (19.6)
Relapse free	112 (79.4)	36 (70.6)
Unknown	4 (2.8)	5 (9.8)
Survival status[c]		
Alive	111 (78.7)	37 (72.6)
Dead	25 (17.7)	11 (21.6)
Unknown	5 (3.6)	3 (5.9)

CINV, chemotherapy-induced nausea and vomiting

[a]As recorded in the medical record. CINV data were not statistically different. [b]As of January 1, 2012. [c]As of June 30, 2012.

TABLE 3 Propensity score weighted regression analysis on the completion of all planned cisplatin[a]

Variable	Odds ratio	95% CI	*P* value
Aprepitant vs no aprepitant	2.3	1.08-5.1	.03
Regional metastases	0.23	0.04-1.16	.07
≥1 comorbidity	0.49	0.2-1.18	.11

CI, confidence interval

[a]Dependent variable is completion of 3 cycles of cisplatin.

TABLE 4 Propensity score weighted Cox regression analysis on recurrence- or progression-free survival[a]

Variable	Hazard ratio	95% CI	*P* value
Aprepitant vs no aprepitant	0.47	0.17-1.28	.04
Patient weight, kg	0.98	0.96-1.0	.06
Metastases			
Regional	9.2	3.3-25.1	<.001
Local	22.8	2.16-240	.009
Surgically treated	3.5	1.38-8.74	.008

CI, confidence interval

[a]Dependent variable is completion of 3 cycles of cisplatin.

TABLE 5 Propensity score weighted Cox regression analysis on overall survival

Variable	Hazard ratio	95% CI	*P* value
Aprepitant vs no aprepitant	1.29	0.36-4.6	.69
Patient weight, kg	0.96	0.94-0.99	.011
Alcohol use	12.3	3.1-49.5	<.001
Regional metastases	108	31-378	<.001
ECOG PS, vs 0			
1	3.2	0.9-11.4	.072
≥2	26.7	7.6-93.7	<.001
Tumor location, vs tongue			
Mouth	0.03	0.01-0.16	
Tonsil	0.12	0.04-0.39	
Larynx	0.03	0.01-0.47	
Other	0.13	0.04-0.38	

CI, confidence interval; ECOG PS, Eastern Oncology Cooperative Group Performance Status

patient-related risk factors for CINV. These include young age (<40 years), female gender, pre-existing anxiety, prechemotherapy nausea, disease stage, and a history of low alcohol consumption.[32-34] In our cohort, the noticeably lower use of alcohol in the aprepitant group suggests that that these individuals may have had a disproportionately higher baseline risk of CINV compared with patients in the control group, thus reducing any apparent intergroup differences that would otherwise have been observed.

Consistent with previous findings, we found additional characteristics that informed prognosis. For instance, an increased burden of disease and poor performance status were associated with worse outcomes, which has been described previously. A history of surgical management posed a greater likelihood or recurrence or progression, whereas a higher baseline weight correlated with lower risk of death. The precise reasons underlying these observations are unclear. However, the difficult anatomy of many HNCs often makes surgery technically difficult to perform. Kraus and colleagues showed that positive surgical margins were prevalent in cases of HNCs and significantly predicted for inferior disease control.[35] Conversely, with respect to the impact of patient weight, McRackan and colleagues demonstrated that being underweight posed a higher risk of earlier disease recurrence (HR, 4.4) and shorter survival (HR, 3.6).[36] A similar association has been observed in other malignancies, including women with advanced or recurrent endometrial cancer and advanced cervical carcinoma.[37,38] It is possible that the higher baseline weight in the aprepitant group may simply be a proxy for better nutritional status and thus resulted in better OS.

This study should be interpreted in the context of several limitations. First, its retrospective nature inherently means that there is potential selection bias whereby patients who are considered to be particularly high risk for CINV may be more likely to be offered aprepitant, whereas those deemed to be at low to moderate risk may not be given aprepitant. However, our use of propensity score adjustments in addition to conventional multivariate models accounted for all measured confounders. Nonetheless, the risk of residual confounding by unmeasured factors remains. Second, our study methods relied heavily on information that was documented in the medical records. Absence of details about nausea or emesis does not imply that the symptom did not occur, particularly for nausea, which is more subjective and prone to underreporting. Likewise, we were unable to reliably ascertain the grade of CINV that was experienced by patients. Finally, although we made every effort to collect recurrence as accurately as impossible, the dates of confirmed recurrences or metastases were invariably dependent on when imaging studies were ordered and when follow-up appointments were conducted.

In conclusion, our data suggest that the use of aprepitant with highly emetogenic chemotherapy was associated with several potential clinical benefits, including a trend towards less emesis. In addition, aprepitant use was correlated with improved adherence to prescribed chemotherapy and contributed to potentially better outcomes. The findings from this study should compel practicing physicians to consider implementing this agent into their antiemetic regimen to optimize control CINV for HNC patients receiving high-dose cisplatin.

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