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Supportive and Palliative Care

Chemotherapy-Induced Nausea and Vomiting in Gastrointestinal Cancer Patients: Do We Need to Revisit Guidelines?

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Abstract

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Purpose The objective of this study was to assess the proportion of patients developing chemotherapy-induced nausea and vomiting (CINV) after receiving chemotherapy for gastrointestinal (GI) cancers, despite receiving antiemetic prophylaxis (AEP) as per the standard guidelines.

Patients and Methods Between April 2019 and March 2020, all patients planned for chemotherapy were eligible for enrolment in the study. The primary endpoint of the study was the assessment of complete response (CR) rates.

Results Overall, 1,276 consecutive patients were screened for this study, while 738 patients fulfilling the eligibility criteria were included. A total of 23.2% of the whole cohort failed to achieve CR. Also, 28.2, 16.9, and 16.6% of patients receiving moderately emetogenic chemotherapy (MEC), low emetogenic chemotherapy (LEC), and high emetogenic chemotherapy (HEC), respectively, failed to achieve CR. The differences in failure to achieve CR was statistically significant between MEC and HEC ($p < 0.001$) groups. Among MEC group, there was no difference between those who received oxaliplatin (27.8%) versus nonoxaliplatin regimens (25.8%) in terms of failure rates ($p = 0.613$).

Conclusion Approximately one-fourth of patients failed to achieve a complete response from CINV in GI cancers despite using guideline-based AEP. Patients receiving MEC had the highest failure rates suggesting a need to improve AEP in these patients.

Keywords
- CINV
- moderately emetogenic chemotherapy
- MEC
- oxaliplatin
- complete response

Introduction

Chemotherapy-induced nausea and vomiting (CINV) is one of the most bothersome adverse effects of cancer chemotherapy and is implicated in reducing the quality of life and altering compliance to treatment.[1] The patients may also develop complications secondary due to CINV, including anorexia, dehydration, and hyponatremia, besides entailing logistic issues.[2] Various guidelines are available with regard to antiemetic prophylaxis (AEP) with the Multinational Association of Supportive Care in Cancer/European Society for Medical Oncology

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(MASCC/ESMO) and American Society of Clinical Oncology (ASCO) are the most commonly followed and cited.[3,4] These classify the potential of CINV as per chemotherapy drug/regimen into high, moderate, and low emetogenic chemotherapeutic (HEC, MEC, and LEC, respectively) regimens. CINV comprises of early and delayed onset, both with their own purported mechanisms.[5]

Gastrointestinal (GI) cancer chemotherapy entails significant use of oxaliplatin and irinotecan in a majority of patients, thereby classifying most regimens as MEC. However, there is limited data assessing CINV in patients with GI cancers. This study focused on GI cancer patients with the primary objective to assess the complete response (CR) rates with existing antiemetic prophylaxis.

Patients and Methods

Eligibility Criteria

Eighteen years or older chemo-naïve patients with GI malignancy and the Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 were eligible for enrolment in the study. Patients with symptomatic brain metastases and psychiatric/cognitive dysfunction, possibly interfering with the compliance to antiemetic therapy or with clinical evidence of current or impending bowel obstruction, were excluded from the study. The patients who were unable to maintain the diary were also excluded.

Study Design and Oversight

This was an observational study in which patients receiving chemotherapy for GI cancers (stomach, pancreas, gallbladder, and colorectal cancers) at Tata Memorial Hospital, Mumbai, between April 2019 and March 2020 were included. Patients were counseled to use a diary to record the number of vomiting episodes, intensity, and duration of nausea in the 5 days of postchemotherapy as part of standard of care in our unit. The primary endpoint of the study was an assessment of CR rates, defined as an absence of vomiting, significant nausea, or the need for rescue medications. The study was conducted in accordance with GCP (good clinical practice) ICH (International Council for Harmonization) and the Declaration of Helsinki principles. Written informed consent was obtained from all patients. The data were collected by trained medical coordinators. The authors vouch for the accuracy and completeness of the data and analysis and for adherence to the study protocol.

Treatment Regimen

The doses of the antiemetic used in the study were as per the standard recommendations and available studies published from India.[4-7]

All participants receiving HEC regimen received a 5HT3 (5-hydroxytryptamine) receptor antagonist (0.25-mg palonosetron intravenously or 1-mg granisetron intravenously, with the specific agent chosen by the primary clinician) on day 1 of chemotherapy, dexamethasone (8–12 mg intravenously on day 1 and 8-mg orally on days 2, 3, and 4), an NK1 (neurokinnin 1) receptor antagonist (125-mg aprepitant orally on day 1 and 80 mg on days 2 and 3, or 150-mg fosaprepitant intravenously on day 1), and olanzapine (10 mg per day orally from day 1–4) in the selected cohort.

All participants receiving an MEC regimen received a two-drug combination of a 5-HT3 receptor antagonist and dexamethasone (8–12 mg intravenously on day 1). The patients receiving carboplatin were also given an NK1 receptor antagonist, and patients with LEC regimen received either a single dose of a 5-HT3 receptor antagonist or a single 8-mg dose of dexamethasone before chemotherapy treatment. The patients receiving minimal emetogenic chemotherapy did not receive any premedication.

It should be noted that carboplatin-based regimens and FOLFIRINOX (modified 5-FU/LV-irinotecan-oxaliplatin) were classified as an MEC regimen.

Statistical Analysis

A descriptive analysis was performed on all of the variables (demographic variables and characteristics of the patients, the disease, and the chemotherapy received). For the primary objective, the incidence of CINV was evaluated during the 5 days following administration. CINV within the first 24 hours following administration of the chemotherapy (acute phase) and during the 4 subsequent days (delayed phase) were recorded and expressed as percentages. Logistic regression analysis was performed to identify significant factors affecting CINV. A p-value of less than 0.05 was considered statistically significant. SPSS version 26 (Armonk, New York, United States) was used for all statistical calculations.

Results

Patients and Demographics

A total of 1,062 cycles of chemotherapy from April 2019 to March 2020 was administered to these patients. Briefly, the median age of the patients was 53 years (range: 18–77 years) with 57.3% being males. Biliary tract cancer (31.7%) was the most common diagnosis followed by colorectal (29.2%) and gastric cancer (19.7%). Out of the 1,062 cycles delivered, 211 (9.8%) were HECs, 613 (57.7%) were MECs, 219 (20.6%) were LECs, while 19 (1.8%) were minimal emetogenic.

Control of Nausea and Vomiting

The rates of CR of CINV during acute and delayed periods are shown in ►Table 1. CR was not achieved in 23.2% of all cycles. CR was not achieved in 28.2% of the MEC regimen cycles, followed by 16.9% of LEC regimen cycles, and 16.6% of HEC regimen cycles. The loss of CR was similar with cycle 1 versus subsequent cycles (►Table 2).

For MEC regimens, the failure to achieve CR rates was not statistically different by gender (p = 0.79) or age group (p = 0.083). Patients treated with oxaliplatin (27.9%) versus those with nonoxaliplatin (26.3%) regimens had similar failure rates overall (p = 0.714). There was no difference in the failure rates of oxaliplatin versus irinotecan-based regimens. Loss of CR was significantly higher for delayed (p = 0.028) and overall CINV (p = 0.017) with

Table 1 Failure to achieve complete response for acute and delayed chemotherapy-induced nausea and vomiting across the chemotherapy cycles as per emetogenic risk groups

	Overall cohort *n* (%)	Minimal risk *n* (%)	LEC regimen *n* (%)	MEC regimen *n* (%)	HEC regimen *n* (%)
Nausea					
Acute	180 (16.9)	2 (10.5)	27 (12.3)	124 (20.2)	27 (12.8)
Delayed	192 (18.1)	1 (5.2)	28 (12.7)	134 (21.8)	29 (13.7)
Vomiting					
Acute	104 (9.8)	0 (0)	13 (5.9)	83 (13.5)	8 (3.8)
Delayed	101 (9.5)	0 (0)	10 (4.6)	78 (12.7)	13 (6.1)
Overall CINV					
Acute	206 (19.4)	2 (10.5)	33 (15.1)	143 (23.3)	28 (13.3)
Delayed	212 (19.9)	1 (5.2)	32 (14.6)	147 (23.9)	32 (15.2)
Overall (acute and delayed)	247 (23.2)	2 (10.5)	37 (16.9)	173 (28.2)	35 (16.6)

Table 2 Comparison of complete response rates (acute, delayed, and overall) for cycle 1 versus cycle 2 and beyond

CR not achieved	Cycle 1 (*n* = 738); *n* (%)	Cycle 2 and beyond (*n* = 324); *n* (%)	*p*-Value[a]
Overall	176 (23.8)	71 (21.9)	0.688
Acute	141 (19.1)	65 (20.0)	0.483
Delayed	156 (21.1)	56 (17.2)	0.191

Abbreviation: CR, complete response.
[a]Pearson's Chi-square test.

the capecitabine-oxaliplatin (CAPOX) regimen (once in every 3 weeks 130 mg/m^2 oxaliplatin) as against the regimens of oxaliplatin using 85 mg/m^2 2 weekly.

The baseline demographics of patients who failed to achieve CR as compared with those who achieved CR in their first cycle of chemotherapy. The significant differences were observed for ECOG performance status and emetogenicity group of chemotherapy on univariate analysis. Logistic regression analysis was performed to ascertain the effects of age, gender, comorbidities, ECOG group, and emetogenicity risk group on the likelihood that patients failed to achieve CR. The logistic regression model was statistically significant, $\chi 2 = 46.5$, $p < 0.001$ (►Table 3). The model explained 9.2% (Nagelkerke's R2) of the variance in CR through the variables included and correctly classified 77.6% of cases. Patients with an ECOG performance score of 2 were 2.1 times more likely to fail to achieve CR than patients with a score of 0 to 1 ($p = 0.011$). Patients with an ECOG performance score of 2 ($p = 0.011$) and moderate emetogenic risk group ($p = 0.006$) significantly predicted the failure to achieve CR.

Discussion

This study was performed to assess the rates of complete control of CINV in 738 GI cancer patients who received 1,062 cycles of chemotherapy on an outpatient basis in daycare of our hospital. A previous study from our institution reported that the proportion of prescriptions, classified as ASCO guideline adherent, and postcorrective measures was 63.6 and 98.5%, respectively.[8] In another study from Japan, Fujii et al reported a significant improvement in complete response from nausea and vomiting during the delayed period from 54 to 74% when the adherence to standard CINV prophylaxis guidelines was ensured.[9] However, in our study, only patients who received CINV prophylaxis as per the standard guidelines were included. Despite adequate prophylaxis, CR could not be achieved in 23.2% of all the chemotherapy cycles. This is higher in comparison to Japanese study by Suzuki et al where they reported CR rates of 96% for no vomiting and 87% for no CINV during the overall period of the first cycle of chemotherapy.[10] This study included only colorectal cancer patients receiving MEC; however, in our study, multi-site GI cancer patients were included. Interestingly, the rates of failure to achieve CR were the highest among patients receiving MEC regimen (28.2%) and this was statistically worse as compared with patients on HEC (16.6%, $p = 0.001$). In the entire cohort, the comparison of failure rates to achieve CR clearly pointed toward higher rates in oxaliplatin-based chemotherapy versus nonoxaliplatin chemotherapy in acute ($p = 0.042$), delayed ($p = 0.034$), and overall ($p = 0.006$) phases of CINV. Nishimura et al tried to evaluate the role of NK1 antagonists in patients receiving oxaliplatin and reported significant benefit of the same.[11,12] Another phase-III study added that NK1 antagonist casopitant intravenous single dose to ondansetron and dexamethasone in MEC regimens failed to show an improvement in CINV rates.[4] Our study reinforces the fact that patients receiving oxaliplatin have higher failure rates and might benefit from additional antiemetic prophylaxis. In the study, presented as abstract by Binder et al, which evaluated 13,330 patients receiving oxaliplatin, the results concluded that there is a differential risk of CINV based on

Table 3 Logistic regression analysis of factors that can affect the complete response rates for moderate emetogenic risk chemotherapy

	Number (n = 601)	Percentage	p-Value
Overall			
Age (y)			0.177
≤60	137/475	28.8	
>60	28/126	22.2	
Gender			0.588
Male	102/385	26.5	
Female	63/216	29.1	
Chemotherapy regimen			0.714
Oxaliplatin based	115/407	28.2	
Nonplatin based	50/190	26.3	

Note: Twelve patients receiving carboplatin were removed from this analysis of moderate emetogenic risk chemotherapy.

age and gender.[13] In our study, there was no effect of gender or age on the CP rates.

An additional finding in our study was that among patients receiving MEC, CR rates of oxaliplatin versus irinotecan regimen were similar. These results are similar to that reported by Iihara et al in which the control of CINV in the first cycle was similar among various MEC regimens, including carboplatin, irinotecan, and oxaliplatin.[14] Thus, it appears that irinotecan- and oxaliplatin-based regimens might benefit from additional antiemetic prophylaxis (NK1 antagonist). In our analysis, oxaliplatin 130 mg/m^2 (3 weekly) appears to be more emetogenic than 85 mg/m^2 (2 weekly). The loss of CR was significantly higher (for delayed and overall CINV) with the CAPOX regimen (130 mg/m^2 oxaliplatin) as against the regimens of oxaliplatin using 85 mg/m^2. But this was not statistically significant when it comes to the acute phase. Hence this difference could be due to capecitabine, and this can be hypothesis-generating to consider CAPOX as multiday requiring additional antiemetic prophylaxis. The addition of NK1 antagonists or olanzapine can be considered for such regimens.[12,15]

Limitations and Strengths

The authors admit that there are some important limitations to this study. The present study was a single-center observational study. However, an important strength of this study was the exclusive patients of GI cancers and the inclusion of all risk groups in the study to provide real-world data.

Conclusion

Around one-fourth of patients failed to achieve complete response for CINV in GI cancers despite using prophylaxis as per standard guidelines. MEC regimen patients had the highest failure rates suggesting the need to revisit the guidelines for these patients.

Informed Consent

Consent was not applicable as data were collected from a prospectively collected database including patient diaries which are the parts of standard of care in our unit.

Authors' Contributions

All authors contributed equally in all aspects.

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None declared.

Conflicts of Interest

None declared.

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