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Research Article

Comparison of Anti-Emetic Efficacy of Granisetron and Dexamethasone Supplemented or not with Aprepitant During Hepatic Arterial Infusion Chemotherapy Against Hepatocellular Carcinoma: A Prospective Controlled Study

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Abstract

Objectives: Controlling chemotherapy-induced nausea and vomiting in patients with unresectable hepatocellular carcinoma (HCC) can be a challenge. Here we explored whether an anti-emetic regimen of granisetron and dexamethasone can be significantly improved by adding aprepitant.

Methods: A total of 246 HCC patients at our medical center were prospectively enrolled between August 2020 and May 2023 to receive granisetron and dexamethasone at 30 min before initiation of hepatic arterial infusion chemotherapy. Just over half the patients (142) also received aprepitant at the same time as granisetron and dexamethasone, then again one and two days later. Patients who received aprepitant or not were compared in terms of the proportion who completed the first chemotherapy cycle without an emetic episode or rescue medication. Secondary outcomes included the proportion who completed all chemotherapy cycles without emetic episode or rescue medication, as well as the frequencies of rescue medication and of chemotherapy interruption due to nausea or vomiting throughout all chemotherapy cycles.

Results: The proportion of patients completing the first cycle without emetic episode or rescue medication tended to be higher when aprepitant was used (79.8% vs 69.7%), but the difference was not significant (p=0.287). A similar result was observed across all chemotherapy cycles (70.2% vs 59.8%, p=0.144). While aprepitant was associated with a significantly lower proportion of patients who required rescue medication (8.6% vs 18.3%, p=0.041), the two groups of patients had to interrupt chemotherapy due to nausea or vomiting with similar frequencies (2.9% vs 4.2%, p=0.737).

Conclusion: Adding aprepitant to the combination of granisetron and dexamethasone may reduce the need for rescue medication against nausea and vomiting among HCC patients receiving hepatic arterial infusion chemotherapy, but this may not translate to clinically significant additional benefit.

Keywords: Aprepitant, anti-emetic efficacy, hepatic arterial infusion chemotherapy, FOLFOX, hepatocellular carcinoma

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Hepatic arterial infusion chemotherapy (HAIC), in which highly concentrated chemotherapy drugs are injected into the tumor via the hepatic artery,[1-3] can improve the prognosis of many patients with unresectable hepatocellular carcinoma (HCC). Particularly effective at prolonging survival is the HAIC regimen known as "FOLFOX": oxaliplatin, fluorouracil, and leucovorin.[2, 4-6] However, FOLFOX and other types of HAIC can induce nausea and vomiting,[7] which lowers patients' quality of life and reduces their compliance with treatment. In the FOLFOX regimen, fluorouracil is weakly emetogenic, while oxaliplatin is moderately so.[8] The optimal anti-emetic regimen for HAIC remains unexplored.

More is known about anti-emetic regimens to counteract nausea and vomiting induced by systemic intravenous or oral chemotherapy. Guidelines from the American Society of Clinical Oncology recommend giving patients on moderately emetogenic chemotherapy the combination of dexamethasone and an antagonist of 5-hydroxytryptamine-3 (5-HT3) receptors such as granisetron.[8] However, such combinations fail to provide satisfactory relief to many colorectal cancer patients treated with oxaliplatin-based chemotherapy regimens like FOLFOX.[9, 10] Guidelines from the National Comprehensive Cancer Network suggest that better efficacy may be achieved by combining these two drugs with a neurokinin receptor antagonist[11] such as aprepitant. Aprepitant prevents substance P from binding to NK-1 receptors in the central nervous system, which can reduce acute and delayed vomiting.[12-15] Combining aprepitant with dexamethasone allows the use of a lower dose of the latter, reducing the risk of dexamethasone-induced hyperglycemia, dyspepsia and insomnia.[16-18]

Whether the recommended combination of dexamethasone and 5-HT3 antagonist can provide adequate anti-emetic efficacy to HCC patients on HAIC is unclear, as are the potential benefits of adding aprepitant to the mix. HAIC involves injection into the hepatic artery, in contrast to systemic administration via a peripheral or central vein. One retrospective study has reported that adding aprepitant to the combination of dolasetron and dexamethasone led to a significantly higher proportion of patients who completed HAIC without emetic episodes or anti-emetic rescue medication, and to significantly lower rates of rescue medication or HAIC interruption due to nausea or vomiting.[19] Therefore we designed a prospective study to verify and extend the exploration of anti-emetic regimens with or without aprepitant for HCC patients receiving HAIC.

Methods

Study Design and Patients

This single-center, prospective study was approved by the Ethics Office of Guangxi Medical University Cancer Hospital (LW2023055) and conducted in accordance with the most recent amendments to the Declaration of Helsinki. Data were collected, analyzed and reported according to STROBE guidelines.[20]

Patients with HCC who were scheduled to undergo HAIC-FOLFOX at Guangxi Medical University Cancer Hospital (Nanning, China) were consecutively enrolled from August 2020 to May 2023, as long as they were 18-75 years old, had been diagnosed with HCC according to recommended criteria,[21] had an Eastern Cooperative Oncology Group Performance Status of 0 or 1, and had a Child-Pugh score of 5-7 points. Patients had to be diagnosed with HCC based on enhanced computed tomography and/or magnetic resonance imaging, regardless of whether the level of alpha-fetoprotein in serum was ≥400 ng/ml. HCC was staged according to the Barcelona Clinic Liver Cancer system.[22] Patients provided written informed consent before enrollment.

Patients were not enrolled if they had ever received systemic chemotherapy; had undergone transarterial (chemo) embolization or taken immunosuppressants within the preceding two weeks; had active infection, body temperature of 38.5 °C or white blood cell count > 15 x 10^9 /L; had a history of alcohol addiction, psychiatric substance abuse or mental disorder; or were pregnant or lactating.

Patients were exited from the study if they took an anti-emetic regimen different from the one stipulated in the trial protocol. Patients were included in the final analysis if their anti-emetic regimen was granisetron and dexamethasone, with or without aprepitant, administered as described below.

HAIC-FOLFOX

The following regimen was administered: oxaliplatin in 5% glucose (250 ml) for 3 h at a dose of 135 mg/m^2 if the tumor had a diameter >10 cm and abundant blood supply, or at a dose of 85 mg/m^2 otherwise; 5-fluorouracil in 0.9% NaCl (250 ml) at a dose of 400 mg/m^2 or calcium-levofolinate at a dose of 200 mg/m^2 for 2 h; and 5-fluorouracil in 0.9% NaCl (100 ml) for 2 h at a dose of 400 mg/m^2 as an arterial infusion, followed by infusion in 0.9% NaCl (230 ml) for 23 h at a dose of 2400 mg/m^2. This regimen was repeated every 3-4 weeks.

Anti-Emetic Regimen

At 30 min before the start of HAIC on day 1, patients received granisetron (3 mg) and dexamethasone (8 mg) in-

travenously. Patients who also took aprepitant received it orally on day 1 (125 mg) and again on days 2 and 3 (80 mg each time).

Data Collection and Outcomes

Data were prospectively collected on patient age, sex, height, weight, smoking, alcohol consumption, type 2 diabetes, hypertension, preoperative indications for HAIC (hepatitis B surface antigen, alpha-fetoprotein, leukocyte count, platelet count, total bilirubin level, albumin level, cirrhosis, liver function classification, tumor stage), number of HAIC cycles as well as incidence and severity of nausea and vomiting and use of anti-emetic rescue drugs during each cycle.

The primary outcome was the proportion of patients who completed the first HAIC cycle without an emetic episode or use of rescue medication. Such medication could include, but was not limited to, metoclopramide, dexamethasone or other hormones, or 5-HT3 receptor antagonists such as granisetron or palonosetron. Secondary outcomes were proportions of patients who completed all HAIC cycles without an emetic episode or use of rescue medication, proportions who experienced nausea and vomiting of a certain severity, as well as the frequency of rescue medication and HAIC interruption due to nausea or vomiting throughout all HAIC cycles. The severity of nausea and vomiting was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0).[23]

Statistical Analysis

Data were analyzed statistically using SPSS 22.0 (IBM, Chicago, IL, USA). Continuous data were reported as mean±SD, and inter-group differences were assessed for significance using Student's t test. Categorical data were reported as n (%), and inter-group differences were assessed using the χ^2 test. Inter-group differences in the frequency of nausea and vomiting and the frequency of HAIC interruption because of nausea or vomiting were assessed using the χ^2 test. All statistical testing in this study was two-sided, and results associated with $p<0.05$ were considered significant.

Results

Our final analysis included 246 HCC patients treated with HAIC-FOLFOX, of whom 104 (42.3%) took aprepitant in addition to granisetron and dexamethasone (Fig. 1, Table 1). Patients who took aprepitant did not differ significantly from those who did not in terms of the proportion who completed the first HAIC cycle without emetic episode or rescue medication, the proportion who completed all HAIC cycles without these events, the frequency of nausea or vomiting across all cycles, and the frequency of vomiting during the first cycle (Table 2). Nevertheless, the proportion of patients who experienced nausea across all HAIC cycles was significantly lower among those who took aprepitant. Most events of nausea or vomiting had a severity of grade 1 or 2, while grade 4 events were not observed.

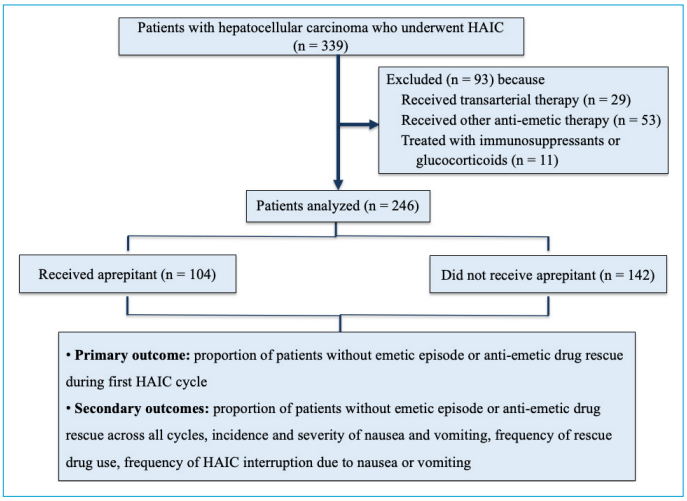

Figure 1. Flowchart of patient enrollment and analysis. HAIC, hepatic arterial infusion chemotherapy.

The proportion of patients requiring rescue medication across all HAIC cycles was significantly lower among those taking aprepitant. On the other hand, similar proportions in the two groups had to interrupt HAIC because of nausea or vomiting.

Discussion

Here we did not observe a significant benefit of adding aprepitant to an anti-emetic regimen of granisetron and dexamethasone among HCC patients receiving HAIC-FOLFOX. This contrasts with a previous retrospective study,[19] also involving Chinese HCC patients, which found that adding aprepitant significantly enhanced the anti-emetic efficacy of the two-drug combination. Our data suggested a trend toward better efficacy among patients receiving aprepitant, which may reflect the fact that its mechanism of action is complementary to that of the other two drugs. Perhaps we would have observed significant benefit with a larger sample. A randomized, double-blind study found that adding aprepitant to ondansetron and dexamethasone reduced vomiting and nausea in patients with a variety of tumor types during early and late phases of moderately emetogenic chemotherapy.[17]

We found that aprepitant tended to decrease the frequency of severe vomiting during the first or all cycles of HAIC, without achieving significant benefit, while it significantly

Table 1. Baseline clinicodemographic characteristics of patients in the study, stratified by whether they received aprepitant in addition to the two-drug anti-emetic regime

Characteristic	Aprepitant (n=104)	No aprepitant (n=142)	p
Female	14 (13.5)	15 (10.6)	0.550
Age, yr	49 (28-65)	51 (26-69)	0.987
Smoking	45 (43.2)	75 (52.8)	0.901
Drinking	43 (41.3)	57 (40.4)	0.896
Hypertension	22 (21.2)	29 (20.6)	1.000
Diabetes mellitus	10 (9.6)	15 (10.6)	0.835
Body mass index, kg/m^2	21.9 (19.9-27.1)	21.8 (19.9-26.8)	0.515
HBsAg	85 (81.7)	120 (85.1)	0.506
Alpha-fetoprotein ≥ 400 ng/mL	54 (51.9)	85 (59.9)	0.251
White blood cell count, x 10^9	6.4 (3.2-13.0)	6.2 (3.3-13.5)	0.906
Platelet count, x 10^9	189 (78-356)	194 (89-473)	0.977
Total bilirubin, μmol/L	15.5 (12.1-33.6)	16.6 (11.7-34.0)	0.622
Albumin, g/L	37.1 (26.8-45.1)	35.9 (27.9-48.9)	0.551
Child-Pugh A	89 (85.6)	121 (85.2)	1.000
Liver cirrhosis	80 (76.9)	119 (84.4)	0.325
Barcelona Clinic Liver Cancer stage			0.599
A	5 (4.8)	9 (6.4)	
B	31 (29.8)	34 (24.1)	
C	68 (65.4)	98 (69.5)	

Values are n (%) or median (interquartile range), unless otherwise noted; HBsAg, hepatitis B virus surface antigen.

Table 2. Comparison of outcomes between patients who received aprepitant or not in addition to the two-drug anti-emetic regime*

Outcome	Grade	Aprepitant, n=104 (%)	No aprepitant, n=142 (%)	p
Nausea during first cycle of chemotherapy	0	79 (76.0)	95 (66.9)	0.256
1	11 (10.6)	28 (19.7)		
2	8 (7.7)	12 (8.5)		
3	4 (3.8)	7 (4.9)		
Nausea across all cycles	0	74 (71.2)	70 (49.3)	0.007
1	16 (15.4)	39 (27.5)		
2	10 (9.6)	21 (14.8)		
3	4 (3.8)	12 (8.5)		
Vomiting during first cycle	0	83 (79.8)	99 (69.7)	0.287
1	14 (13.5)	24 (16.9)		
2	5 (4.8)	14 (9.9)		
3	2 (1.9)	5 (3.5)		
Vomiting across all cycles	0	73 (70.2)	85 (59.8)	0.144
1	22 (21.2)	30 (21.1)		
2	7 (6.7)	20 (14.1)		
3	2 (1.9)	7 (4.9)		
Rescue medication		9 (8.6)	26 (18.3)	0.041
Chemotherapy interruption due to nausea or vomiting		3 (2.9)	6 (4.2)	0.737

* Values indicate the number (%) of patients who experienced at least one occurrence of the indicated outcome.

decreased the frequency of nausea of any severity. These results contrast with the idea that aprepitant is more effective at preventing vomiting than nausea,[17, 24, 25] and they support the usefulness of addressing both problems simultaneously during anti-emetic therapy.[26]

It may be possible to further optimize a triple-combination anti-emetic regimen for HCC patients on HAIC-FOLFOX. For example, palonosetron may be superior to granisetron for reducing nausea and vomiting in both early and late phases of chemotherapy.[27, 28] Timing of the anti-emetic drug administration relative to the start of chemotherapy may also make a difference, which we did not explore here. In any case, different anti-emetic regimes may need to be optimized for chemotherapy involving more strongly emetogenic drugs. For example, a regimen involving fosaprepitant, ondansetron, dexamethasone and the antipsychotic olanzapine appears to be effective against strongly emetogenic multiday chemotherapy based on cisplatin.[29] HAIC interruption due to nausea or vomiting was relatively infrequent in our study, emphasizing that our findings may not be generalizable to more emetogenic chemotherapy regimens.

Indeed, our results involving patients from a single center on a single type of chemotherapy should be verified and extended in large, multi-center trials that allow for appropriate subgroup analyses. Such work should aim to adjust for potential confounding by factors that may affect anti-emetic efficacy, such as sex, age, and use of tobacco and alcohol.

Disclosures

Ethics Committee Approval: The study was retrospectively approved by the Guangxi Medical University Cancer Hospital Ethics Committee in April 27, 2023 (LW2023055).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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