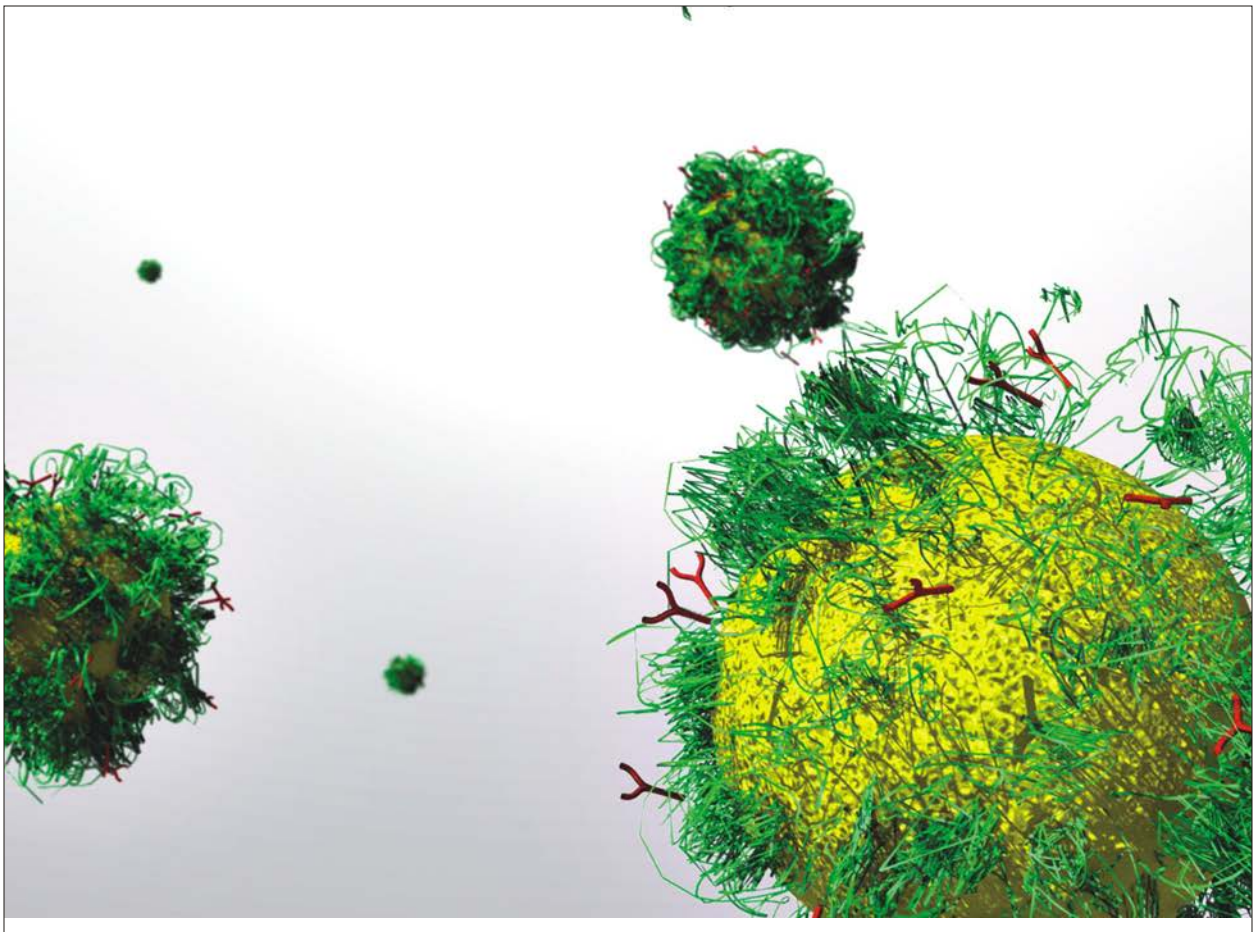

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Research Article
Comparative Emetogenicity Study of Cisplatin Alone and in Combination Regimen on Cancer Patients of Bangladesh

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Abstract

Background and Objective: To compare the prevalence of acute vomiting between patients receiving cisplatin as monotherapy or cisplatin in a combination regimen. **Materials and Methods:** The study was conducted at Delta Hospital Dhaka on a total of 70 patients (44 male and 26 female). The patients received either cisplatin alone or cisplatin with the following chemotherapeutic agents-docetaxel and 5 fluorouracil, docetaxel, etoposide, doxorubicin and capecitabine. The study was conducted in patients receiving chemotherapy for a total of the first 3 cycles. The patients were told to record the number of episodes of vomiting they experienced during the first 24 h after chemotherapy at each cycle. All 70 patients received prechemotherapy antiemetics a combination of $5HT_3$ receptor antagonist (ondansetron or palanosetron) and dexamethasone prior to chemotherapy. **Results:** In patients receiving the combination chemotherapy of cisplatin+docetaxel+5 FU experienced the lowest incidence of acute vomiting and cisplatin+capecitabine receiving patients experienced highest incidence of acute vomiting. All the other combination therapy resulted in emesis comparatively similar to that of cisplatin. In all the regimens except for cisplatin+etoposide the percentage of patients experiencing acute vomiting reduced along with progressive cycles. **Conclusion:** When cisplatin is given in combination regimen except for the combination regimen of cisplatin+capecitabine there is no significant increase in emesis between patients receiving cisplatin alone or in combination therapy.

Key words: Cisplatin, acute vomiting, nausea, cancer, docetaxel, 5 fluorouracil, combination regimen

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Chemotherapy has played a fundamental role in cancer therapy for a very long time. Although, these agents have enabled cancer patients to survive longer, they are notorious for having a number of side effects. One of the most feared and agonizing side effects faced by patients undergoing chemotherapy is nausea and vomiting[1,2]. About 80% of the patient experiences chemotherapy induced nausea and vomiting[3] and nausea had been reported to be the most clinically significant side-effect for patients undergoing chemotherapy[4].

Chemotherapy induced nausea and vomiting (CINV) has been distinguished into three different categories based on their period of onset[5]. Acute CINV describes the occurrence of nausea and vomiting during the first 24 h of chemotherapy administration. Delayed CINV refers to nausea and vomiting beginning after the first 24 h of chemotherapy administration and which persists for 5 days following chemotherapy administration. Anticipatory CINV is usually the learned or conditioned response that usually occurs before the beginning of the second cycle or later cycles of chemotherapy. It is a response for poorly managed nausea and vomiting the patient experiences during the earlier cycles.

Chemotherapeutic agents initially had been classified into five categories (Level 1-5) based on their intrinsic ability to induce emesis[6]. Level 5 represents those antineoplastic agents having the highest possibility of inducing emesis and level 1 agents represents those agents with the lowest possibility of inducing emesis. The 5 level classifications was subsequently modified to a 4 level classification system by combining level 3 and 4 together and the agents in this class were denoted as moderately emetogenic. Apart from the classification schema an algorithm had also been established for combination chemotherapy regimen according to which the emetogenicity of chemotherapeutic agents increases when they are given with certain other chemotherapeutic agents in combination[7].

In Bangladesh, there are an estimated 1.3-1.5 million cancer patients and every year around 0.2 million people are diagnosed with cancer[8]. The top five leading cancers are cancer of the lungs, breast, cervix, oral cavity and esophagus for both sexes while lung cancer ranks the most common cancer type for males and breast cancer for females[9]. Cisplatin (cis-dichlordiammine platinum II) is the prototype of a group of drugs called platinum-containing coordination complex[10], which is in use since 1978. It is one of the most potent chemotherapeutic agent that is widely used in the treatment of various types of cancers like carcinoma of the testis, ovaries, cervix, small cell and non-small cell lung cancer[11,12]. In terms of emetogenic potential cisplatin has been classified as a highly emetogenic agent which can provoke nausea and vomiting in 90% of patients without proper antiemetic prophylaxis during the first 24 h of chemotherapy treatment (Acute CINV)[6,7,13]. The emesis observed in cisplatin based chemotherapy occurs in a biphasic manner, with an initial onset of emesis 4-5 h after receiving cisplatin and the second phase starts between 21-24 h following chemotherapy[14]. The present study was conducted to evaluate and compare the incidence of acute vomiting in patients receiving cisplatin in single and in combination regimen to assess whether there is an actual increase in the incidence of acute emesis when cisplatin is given in combination regimen as it has been stated in the algorithm.

MATERIALS AND METHODS

Study design and location: This was a prospective cohort study that was conducted on patients visiting Department of Oncology for receiving chemotherapy at Delta Medical College from July, 2014 to January, 2015. Delta Medical College is a teaching hospital located at Dar-us-Salam road Dhaka.

Ethical aspects: Initially an application to conduct the study along with a sample of the survey questionnaire was sent to the ethical committee of Delta Medical College. The study was reviewed and approved by the ethical committee of Delta Medical College.

Patients and selection criteria: The study was conducted on 70 patients (44 male and 26 female). To be eligible to be included in the study patients had to be at least 18 years old receiving either cisplatin alone or cisplatin in combination therapy. Patient exclusion criteria included those patients who received nutrition by Total Parenteral Nutrition (TPN) and patients with history of motion sickness.

Data collection: A questionnaire was prepared to collect data of the patients. Initial data that was collected from the patients included their age, sex, type of cancer, cancer stage, chemotherapy the patient was receiving, dose and the type and dose of antiemetic that was given prior to the initiation of chemotherapy. The patients were advised to record the number of episodes of emesis they had during the first 24 h.

Statistical analysis: The information obtained was expressed in the form of percentage or mean where appropriate. Relative Risk (RR) was used to determine the prevalence of acute vomiting between patients receiving cisplatin single and

cisplatin in combination regimen. The results of RR were also expressed in terms of 95% Confidence Interval (95% CI).

RESULTS

This was a prospective cohort study that was conducted at Delta Hospital Dhaka on patients receiving cisplatin single or combination therapy. A total of 74 patients received cisplatin therapy but 4 patients (3 female and 1 male) had to be excluded from the study due to a history of motion sickness. Out of the 70 patients, 44 (63%) were male and 26 (37%) were female. The patients were between the ages of 18-76 years with a mean age of 53.4 years. The patients received chemotherapy with any one of the following 6 regimens: Cisplatin alone or cisplatin with a combination of docetaxel+5 fluorouracil, docetaxel, doxorubicin, etoposide or capecitabine. All patients prior to their chemotherapy received dual combination antiemetics which included $5HT_3$ receptor antagonist (Ondansetron or palanosetron) and the corticosteroid dexamethasone (Table 1). The prevalence of acute vomiting in patients receiving cisplatin alone is presented in Table 2. Nearly half of the patients (47.6%) receiving cisplatin experienced vomiting within the first 24 h of chemotherapy. However, the incidence of emesis in patients decreased during the 3rd cycle of chemotherapy (33.3%). Table 3 shows the prevalence of acute emesis for cisplatin combination regimen. In combination regimen the lowest incidence of acute emesis was observed for patients receiving a combination of cisplatin+docetaxel+5 fluorouracil. The incidence of emesis in this group was even lower than that of cisplatin for all 3 cycles (cycle 1: 20%, RR: 2.38, 95% CI: 1.42, 3.95, cycle 2-13.3%, RR-3.57, 95% CI-2.19, 5.83, cycle 3-13.3%, RR-2.5, 95% CI-1.52, 4.08). In the combination regimen of cisplatin+etoposide the patients experienced a lower incidence of acute emesis (40%) compared to cisplatin (47.6%) for the first 2 cycles. The combination regimen of cisplatin+docetaxel and cisplatin+doxorubicin caused acute emesis in patients which was slightly greater than cisplatin

Table 1: Patient demographics and clinical characteristics

Variables	Total patient (N = 70)
Gender	
Male	44 (63%)
Female	26 (37%)
Age range	18-76
Mean age (Mean±SD)	53.4±13.7
Cancer diagnosis	
Lung	19 (27.1%)
Stomach	16 (22.9%)
Cervix	15 (21.4%)
Larynx	7 (10%)
Tongue	4 (5.7%)
Testis	3 (4.3%)
Others	6 (8.6%)
Chemotherapeutic agents	
Cisplatin	21 (30%)
Cisplatin+docetaxel+5FU	15 (21.4%)
Cisplatin+docetaxel	10 (14.3%)
Cisplatin+doxorubicin	6 (8.6%)
Cisplatin+etoposide	10 (14.3%)
Cisplatin+capecitabine	8 (11.4%)
Pre-chemotherapy antiemetics	
Ondansetron+dexamethasone	66 (94.3%)
Palanosetron+dexamethasone	4 (5.7%)

Value in parentheses indicates percentage of the population

Table 2: Prevalence of acute vomiting in patients receiving cisplatin monotherapy

Chemotherapy	Cycle	Total patients	No. of patients with acute vomiting	Patients with acute vomiting (%)
Cisplatin	1	21	10	47.6
	2	21	10	47.6
	3	21	7	33.3

Table 3: Prevalence of acute vomiting in patients receiving cisplatin combination regimen

Chemotherapy	Cycle	Total patients	Patients with acute vomiting	Patients with acute vomiting (%)	RR	95% CI
Cisp+doce+5FU	1	15	3	20	2.38	1.42, 3.95
	2	15	2	13.3	3.57	2.19, 5.83
	3	15	2	13.3	2.5	1.52, 4.08
Cisp+doce	1	10	5	50	0.95	0.59, 1.52
	2	10	4	40	1.19	0.74, 1.92
	3	10	4	40	0.83	0.58, 1.18
Cisp+doxo	1	6	3	50	0.95	0.63, 1.42
	2	6	3	50	0.95	0.63, 1.42
	3	6	2	33.3	1	
Cisp+etop	1	10	4	40	1.19	0.74, 1.91
	2	10	4	40	1.19	0.74, 1.92
	3	10	4	40	0.83	0.58, 1.18
Cisp+cape	1	8	7	87.5	0.54	0.35, 0.83
	2	8	6	75	0.63	0.40, 0.97
	3	8	6	75	0.44	0.25, 0.74

Cisp: Cisplatin, doce: Docetaxel, 5FU: 5 flurouracil, doxo: Doxorubicin, etop: Etoposide, cape: Capecitabine, RR: Relative risk

regimen. However, in both the regimens, the incidence of vomiting decreased in the progressive cycles of chemotherapy and in cisplatin+doxorubicin regimen in the 3rd cycle the percentage of patients experiencing emesis was similar to the patients of cisplatin single regimen (33.3%, RR-1). Out of the 6 different regimens of cisplatin, cisplatin+capecitabine produced the highest incidence of acute vomiting in patients. 87.5% of the patients experienced vomiting in the first 24 h in cycle 1 (RR-0.54, 95% CI-0.35, 0.83). This was significantly higher compared to any other regimens. Just like the other chemotherapy regimens in this combination also emesis decreased in the subsequent 2nd and 3rd cycles however the percentage of patients experiencing acute vomiting was much higher compared to all the other regimens (Cycle 2-75%, RR-0.63, 95% CI-0.40, 0.97, cycle 3-75%, RR-0.44, 95% CI-0.25, 0.74).

DISCUSSION

Prevention of chemotherapy induced nausea and vomiting (CINV) still remains one of the major challenges to overcome in clinical settings for healthcare professionals. Failure to control emesis prior chemotherapy in patients will not only decline their adherence towards the treatment which might further lead to deterioration of their health[15] it will also significantly affect the patient's quality of life[16,17]. The severity and extent to which a patient experiences CINV depends on a number of factors. Apart from the intrinsic emetogenicity of the cytotoxic agent the risk factors includes age, sex, alcohol consumption and history of motion sickness[18-20]. Based on the period of onset, chemotherapy induced emesis can be classified as acute (before 24 h) and delayed (after 24 h). This phase differentiation of emesis is important because prevention of acute emesis appears to reduce the subsequent risk of developing delayed vomiting[21,22].

The intent of our prospective study was to compare the incidence of acute emesis between patients receiving cisplatin alone with those patients receiving cisplatin in combination with other chemotherapeutic agents. Cisplatin is taken to be the archetype antineoplastic agent based on which the emetogenicity of other antineoplastic agents are assessed[23]. Studies has shown cisplatin induced delayed vomiting is less intense than acute vomiting[24]. A number of studies had been conducted on this platinum drug however to the best of our knowledge no such study has been published comparing the emetogenicity of cisplatin when given alone and in combination. The results of this study have not been in accordance with the proposed algorithm.

The most striking findings of this study was when cisplatin combinations are given the acute emesis is not always increasing rather in the combination regimen of cisplatin+docetaxel+5 fluorouracil we had seen a decline in the emetogenesis level amongst the patients. Only when cisplatin is given with capecitabine there is a very high level of emesis in patients. Capecitabine is an oral antineoplastic agent, which is generally referred to as a low emetogenic agent[25], however when it is given in combination along with cisplatin the number of patients experiencing emesis in the first 24 h is greatly increased. For other combination regimen acute vomiting did not increase that significantly. The proposed algorithm[6,7] which stated when any level 2-4 agents are given along with highly emetogenic drug like cisplatin, the overall emetogenicity of the combination is increased to greater extent however from this study what we observed was combination regimen not always increases the emetogenicity in patients.

A number of major organizations namely ASCO, MASCC, ESMO and NCCN have developed certain practicing guidelines regarding the use of antiemetics for patients receiving chemotherapy. According to the most recent guidelines a three-drug regimen consisting of $5HT_3$ receptor antagonist, dexamethasone and neurokinin 1 receptor antagonist aprepitant has been recommended to prevent acute emesis in patients receiving highly emetogenic antineoplastic agents[26-28]. Numerous studies had been conducted on patients receiving cisplatin where it was found addition of the novel antiemetic aprepitant provided a superior antiemetic protection compared to patients receiving a standard dual antiemetic therapy with of $5HT_3$ receptor antagonist and dexamethasone[29-31]. None of the patients in our study had received aprepitant prior to chemotherapy. Thus the introduction of aprepitant in the prechemotherapy antiemetic regimen might bring down the number of patients experiencing acute vomiting.

Despite the number of findings from this study, which is came up with certain number of limitations. This study was conducted on a population which was a convenience sample as it had been done in only one hospital of Dhaka city and not including cancer patients from all over Bangladesh. Due to this limitation the sample size of this study was also comparatively small. Another potential limitation was the emesis had been self-reported by the patients giving a chance for biased or inaccurate results. However, keeping in mind of these limitations this study had served our purpose as we can see and compare the scenario for the occurrence of acute vomiting amongst patients receiving cisplatin with those receiving cisplatin combination.

CONCLUSION

From this study it was found the incidence of acute vomiting between patients receiving cisplatin alone or in combination to be similar except for certain combination regimens. However, a more detailed study needs to be conducted through collaboration of a number of hospitals and including a large patient population to support and confirm the findings of this study.

SIGNIFICANCE STATEMENTS

Cisplatin can be considerd as one of the most effective anticancer agents widely used in the treatment of different types of neoplasms including head and neck, lung, ovarian, leukemia, breast, brain, kidney and testicular cancers. However, cisplatin chemotherapy is also associated with substantial side-effects that include hepatotoxic, nephrotoxic, cardiotoxic, neurotoxic and/or hematotoxic damage. Also, some patients may relapse from cisplatin treatment with their cancers being refractory to cisplatin regimen. Hence, combination therapies of cisplatin with other drugs are common practice in the treatment of human cancers. Findings of this study have suggested that other compounds combined with cisplatin constitute the best therapeutic approach to overcome drug resistance and reduce the undesirable side effects as acute vomiting.

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