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Addition of 3-day aprepitant to ondansetron and dexamethasone for prophylaxis of chemotherapy-induced nausea and vomiting among patients with diffuse large B cell lymphoma receiving 5-day cisplatin-based chemotherapy

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ABSTRACT

Background: Neurokinin-1 receptor antagonists, such as aprepitant are currently emerging as powerful prophylactic agents for chemotherapy-induced nausea and vomiting (CINV). Therefore, it is important to adjust the anti-emetic regimens based on personal risk factors of the patient, duration of the chemotherapy regimen and cost-effectiveness.

Purpose: To determine the efficacy of the 3-day aprepitant along with ondansetron and dexamethasone in controlling CINV in patients with large B cell lymphoma receiving multiday-cisplatin regimen chemotherapy.

Methods: This is a pilot prospective cross-over trial. Patients were allocated to either aprepitant 125 mg on day 1 and 80 mg on days 2 & 3 or placebo in the first 2 cycles, with crossover to the opposite treatment in the 3rd and 4th cycles. The primary end point was complete response (CR) of both acute (days 1–5) and delayed (days 6–8) CINV. CR means neither to develop emetic episodes nor to use rescue anti-emetics medication.

Results: Twelve of the 15 patients recruited for the study were fully evaluable and completed 4 cycles of ESHAP regimen with a total of 48 cycles given. In the cycles with aprepitant and those without the CR were 83.3% and 0% respectively ($p < 0.05$). Patients receiving aprepitant in the first 2 cycles recorded less nausea in subsequent cycles that were given without aprepitant. This was not statistically significant.

Conclusion: This triple anti-emetic regimen showed efficacy in controlling the multi-day cisplatin-induced nausea and vomiting. Further randomized controlled trials are needed to compare between 3-day and 7-day aprepitant for multi-day cisplatin regimens.

Introduction

Chemotherapy-induced nausea and vomiting (CINV) is still among the most distressing adverse effects of chemotherapy. The introduction of neurokinin-1 receptor antagonists (NK1RA), such as aprepitant achieves a major advance in the prevention of CINV especially the delayed type. The next era of anti-emetic research shall aim to tailor the prophylactic anti-emetic regimens based on personal risk factors of the patient, duration of the chemotherapy regimen and cost-effectiveness especially in developing countries. Optimizing the dosage of NK1RA is a crucial step now as it was with metoclopramide that once yielded a favorable effect against CINV only when the dose was escalated massively.

Since their fortuitous discovery in the 1960s, platinum based-compounds, such as cisplatin have sprouted vastly in the armamentarium of anti-cancer drugs. Nowadays, multi-day cisplatin is the cornerstone in treatment of germ cell tumors. Moreover, a regimen entailing multi-day cisplatin along with etoposide, methylprednisolone, high-dose cytarabine, known as ESHAP, has been shown to be active against refractory or relapsed non-Hodgkin's lymphoma (NHL) [1,2].

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The evidence mounts that triple anti-emetic regimen including NK1-RA, 5-hydroxytryptamine-3 receptor antagonist (5HT3-RA) and dexamethasone is the standard of care for prevention of CINV in patients receiving highly emetogenic chemotherapy with single-day cisplatin combination chemotherapy [3]. Despite this significant progress, CINV continues to represent a challenge with multi-day cisplatin settings with a handful of studies that has been conducted till now [4,5]. Therefore, we conducted a pilot cross-over study that compared aprepitant to placebo combined with standard antiemetic prophylaxis (a 5HT3-RA and dexamethasone) in patients receiving 5 days of cisplatin combination chemotherapy for relapsed/refractory NHL aiming to assess the effect of addition of the 3-day aprepitant in preventing delayed CINV.

Patients and methods

Study design

This prospective placebo-controlled cross-over study was conducted in the Clinical Oncology department, Faculty of Medicine, Cairo University between January 2015 and June 2015, after approval by institutional review board. This is a single-blinded double arm trial. Eligible patients were those with relapsed/refractory NHL receiving ESHAP combination chemotherapy. Antiemetic prophylaxis with ondansetrone 8 mg and dexamethasone 8 mg was administered once daily on days 1 to 5. Patients were randomly assigned to either aprepitant 125 mg on day 1 and 80 mg on days 2 & 3 or placebo in the first 2 cycles, with crossover to the opposite treatment in the 3rd and 4th cycles. Treatment group assignments were made by block randomization. Patients served as their own controls with cross-over after two chemotherapy cycles. Cross-over was allowed on systematic basis. The primary end point of the trial is to reach complete response (CR) of both acute (days 1 through 5) and delayed (days 6 through 8) CINV. This means neither to develop any emetic episodes nor to use any of rescue anti-emetics medication. Secondary end point was patient-stated preference after the 4th cycle.

Patients

Inclusion criteria comprised patients age 18 years or older with a diagnosis of relapsed/refractory NHL receiving ESHAP chemotherapy regimen. ESHAP is administered as follows: Etoposide 40 mg/m^2/day as a 1 h intravenous infusion from day 1 to 4; Cisplatin 25 mg/m^2/day as a continuous infusion from day 1 to 4; Solumedrol 500 mg/day as a 15 min intravenous infusion from day 1 to day 5, Cytarabine 2 g/m^2 given as a 2 h intravenous infusion on day 5. Patients must have had no nausea or vomiting for 24 h before study entry and no antiemetic use for 72 h before study entry. Adequate full blood count, Kidney and Liver functions were required.

Response evaluation

A patient diary was given to the members of the study group on cycles 1–4. The diary encompassed days 1 through 8 of their chemotherapy cycle. Each member accomplished a daily record of his/her episodes of nausea and vomiting and the time. Adequate training was provided to participants based on the CTCAE criteria to assess Nausea and Vomiting events. Moreover, any medication taken to control established nausea or emesis i.e. rescue therapy was also recorded. The rescue therapy was determined based on the investigator's choice.

Statistical analysis

Statistical analyses of the data were conducted using small stata 12.1 software for windows. The comparison of the rate of emetic episodes in the placebo and aprepitant cycles was done by Chi-squared test. P-value of <0.05 was considered statistically significant.

Results

Fifteen patients were randomly assigned to one of the two treatment groups. The median age was 45 years (range 38–56 years) with 8 males and 7 females. Twelve of the 15 patients who entered the study were fully evaluable and completed 4 cycles of ESHAP chemotherapy regimen with a total of 48 cycles given, three patients were excluded due to loss of follow up or protocol violation.

The complete response (CR) was 83.3% in the treatment group and 0% in the control group. During the 24 cycles received with aprepitant, nausea was recorded in 3 times (12.5%) compared to 14 times (58.3%) in the cycles without ($p = 0.001$). The median duration was the same between the 2 groups (2 days, range 1–4). Patients receiving aprepitant in the first 2 cycles recorded less nausea in subsequent cycles given without aprepitant compared to the other group without reaching statistical significance (relative risk of 0.75, 95% Confidence interval 0.37 to 1.49). As regarding vomiting, it was recorded once during the cycles with aprepitant (8.3%) compared to 10 times (41.6%) during cycles without aprepitant ($p = 0.002$). Moreover, all participants showed a preference to the cycles with aprepitant.

Discussion

Diffuse large B-cell lymphoma (DLBCL) is one of the most common malignancies among the non-Hodgkin's lymphoma spectrum and is the most common in Egypt. Addition of Rituximab to standard anthracycline-containing regimen significantly improved the disease free as well as overall survival [6]. Nevertheless, one-third of patients still have a disease that is either refractory to initial therapy or relapses after standard therapy [7].

From a patient's perspective, nausea and vomiting are one of the most distressing adverse effects of chemotherapy [8]. The combination of Dexamethasone, with Ondansetron increased the efficacy of Ondansetron in preventing acute CINV by 10–15% in randomized trials but with less success for delayed CINV [9–11]. Aprepitant demonstrated efficacy against both acute and delayed emesis [12].

Nowadays, the expedition for abrogation of emetogenic effect of cisplatin does not only include addition of new drugs or herbals with anti-emetic effect, such as olanzapine and Zingiber officinale [13] but also tailoring the already-validated regimens along with introducing non-pharmacologic solutions, such as acupuncture [14]. This study evaluated the addition of Aprepitant administered on days 1–3 of chemotherapy for acute and delayed CINV prophylaxis in multiday highly emetogenic chemotherapy regimen with standard antiemetic prophylaxis in a randomized, cross-over study design. The study accomplished its primary objective of showing that 3-day aprepitant combined with ondansetron and dexamethasone resulting in a significant improvement in control of CINV in patients receiving 5-day cisplatin-based chemotherapy regimens for relapsed/refractory NHL. Further investigations are needed to prove cost-effectiveness of this regimen and that 3-day aprepitant is non-inferior to 5-day aprepitant. Moreover, patients showed a preference for cycles with aprepitant as it was well tolerated with