Abstract. Aim: To evaluate the efficacy of reduction of dexamethasone with a single-dose of palonosetron in preventing acute and delayed nausea and vomiting in patients receiving highly emetogenic chemotherapy (HEC) for early breast cancer.

Patients and methods: Chemotherapy-naive patients with breast cancer were given HEC in an adjuvant or neoadjuvant setting. Palonosetron and dexamethasone 4 mg i.v. were given on day 1 and another two administrations of dexamethasone 4 mg i.m. were given on days 2 and 3. The end-point was complete response (CR) and complete control (CC) during the acute and delayed phases. Results: Twenty-six patients were observed. Complete response was achieved in 19 out of 26 patients (72.4%); the same result was shown in 72.4% out of 76 courses given. Conclusion: This alternative schedule suggests efficacy for the control of acute and delayed emesis in moderately emetogenic chemotherapy. Further investigations are required to confirm these results.

Nausea and vomiting are common side-effects associated with systemic chemotherapy and are among the adverse effects most feared by patients (1, 2). Although these complications of treatment are usually self-limiting, the deleterious effects on nutritional status and quality of life can be substantial. The onset of emesis and nausea is expected at 0-24 hours, acute phase, and at 24-120 hours, delayed phase, after administration of chemotherapy (3, 4). Different chemotherapeutic agents have different emetogenic potential and their combination increases the grade of emesis, so that anthracycline-based regimens (epidoxorubicin and cyclophosphamide; 5-fluorouracil, epidoxorubicin and cyclophosphamide; 5-fluorouracil, doxorubicin and cyclophosphamide) in patients with breast cancer are now considered as highly emetogenic chemotherapies (HEC).

Antiemetic therapy has dramatically improved during the past twenty years. With optimum treatment, most patients receiving chemotherapy do not experience any nausea or vomiting during the first 24 hours after treatment and at the delayed phase. According to current guidelines, the standard approach for antiemetic prophylaxis in patients treated with HEC is the combination of a 5-hydroxytryptamine receptor (5-HT3) antagonist and dexamethasone with or without neurokinin-1 antagonist on day 1. Serotonin 5-HT3 antagonist plus steroid is required in preventing acute emesis and neurokinin-1 antagonist as a single agent on days 2 and 3.

Palonosetron (Aloxi®) is a unique second-generation 5-HT3 antagonist with a long half-life (about 40 hours) that is structurally unrelated to first-generation 5-HT3 receptor antagonists (dolasetron, ondansetron, tropisetron, granisetron) (5-8). A dose reduction of dexamethasone is needed when palonosetron is used for antiemetic prophylaxis.

The aim of this study was to evaluate the efficacy of a further reduction of dexamethasone with a single-dose of palonosetron in preventing acute and delayed nausea and vomiting in patients receiving HEC for early breast cancer.

Patients and Methods

From November 2011 to September 2012, patients with early or locally advanced breast cancer were selected for the study. They had to be chemotherapy-naive, with histologically-confirmed breast cancer,
and scheduled to receive moderately emetogenic adjuvant or neoadjuvant treatment. Further eligibility criteria were age ≥18 years, performance status 0-1, absolute neutrophil count >1,500/μm³, platelet count >100,000/μm³, liver function ≤2 times the upper limit of normal for liver transaminases) and kidney function (creatinine <1.5 times the upper limit of normal).

Patients were treated with FEC (5-fluorouracil at 600 mg/m², epirubicin at 90 mg/m² and cyclophosphamide at 600 mg/m² every three weeks) or EC (epirubicin at 90 mg/m² and cyclophosphamide at 600 mg/m² every three weeks).

A single intravenous bolus of 0.25 mg palonosetron 30 min before chemotherapy, followed by dexamethasone 4 mg i.v. was given on day 1. Another two administrations of 4 mg dexamethasone i.m. were given on days 2 and 3.

Complete response (CR) was defined as no emetic episodes and no use of rescue medication during the overall study period. Complete control (CC) was defined as no emetic episodes, no use of rescue medication and no more than mild nausea. Partial response (PR) was considered as no more than one emetic episode and no more use than two days of rescue medication. Presence of severe nausea of no more than two days and needs of rescue medication was defined as partial control (PC).

Patients were asked to fill out a diary from days 1 to 4, reporting the emesis episodes, nausea and its severity, and the use of rescue medication (metoclopramide and/or dexamethasone). Patients who took part in the study were observed for a minimum of one up to a maximum of four courses of chemotherapy.

From the beginning of the study, patients were given a diary for each cycle, in which they were required to record every incidence of nausea and/or vomiting that occurred within the first 24 h and from the second to the fifth day after chemotherapy.

Relevant information on the characteristics of each patient, such as the type of chemotherapy, the antiemetic therapy used, with dosage and mode of administration, and any concomitant therapies being given, were recorded in a corresponding file.

The primary aim of the study was to analyze the prevention of delayed emesis in the first cycle, while the secondary aim was to evaluate successive cycles.

Results

Between November 2011 and September 2012, a total of 26 (one male breast cancer only) patients were studied (Table I). The median ECOG performance status was 0 and median age 58 years (42-76 years); 23 out of 25 patients (92%) were of post-menopausal status and only two patients (8%) of pre-menopausal status. Fourteen out of 26 patients (53.8%) were treated with EC, nine out of 26 (34.7%) with FEC in an adjuvant setting, and three out of 26 (11.5%) with EC in a neoadjuvant setting, respectively. At the end of observation, all the patients were available for analysis.

For the first course, CR and CC was observed in 19 out of 26 patients (72.4%) and during the overall acute and delayed phases, PR and CC in three out of 26 patients (11.5%), PR and PC in three out of 26 patients (11.5%), respectively. One patient (3.9%) did not respond to prophylaxis (Figure 1).

The results for a total of 76 courses of chemotherapy given showed CR and CC in 55 courses (72.4%) during the overall phase, PR and CC in 6 cycles (7.9%), PR and PC in 3 cycles (3.9%), CR and PC in 11 courses (14.5%), respectively. There was no control of emesis in 1 (1.3%) of courses (Figure 2).

Rescue antiemetic medication with 4 mg dexamethasone and 10 mg metoclopramide i.m. twice a day was given at patient’s request during the overall study period.

There were no cases of constipation, and abdominal pain and insomnia were not reported. There were no significant changes observed in blood glucose levels, even in five out of 26 patients (19.2%) with type-2 diabetes mellitus, thus no need for changing their therapy came up (Figure 3).

Discussion

Significant improvements in the management of chemotherapy-induced nausea and vomiting (CINV) have occurred in the past 20 years, but these symptoms remain a significant issue in patients with breast cancer undergoing anthracycline-based regimens.

Novel anti-CINV regimens involving the use of antiemetic agents are currently being evaluated in certain patient subpopulations to understand whether different treatment approaches can offer additional protection against the debilitating impact of acute or delayed CINV or similar protection with a simplified antiemetic regimen.

The recent Perugia conference for the antiemetic guidelines suggested the use of palonosetron as the preferred 5-HT3 receptor antagonist in antiemetic therapy for HEC, with administration of dexamethasone during days 2 and 3 after chemotherapy, so that steroid reduction could be useful for selected patients (9).

Patients with type-2 diabetes mellitus, those prone to osteoporosis, and elderly patients can benefit from a lower dose of dexamethasone due to difficulty in controlling sugar levels, and negative impact of steroids on bone regeneration (10-12).

Table I. Patients’ characteristics.  

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n=26*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>58 (42-76)</td>
</tr>
<tr>
<td>Median ECOG PS</td>
<td>0 (0-1)</td>
</tr>
<tr>
<td>Pre-menopausal status, n</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Post-menopausal status, n</td>
<td>23 (92%)</td>
</tr>
<tr>
<td>Adjuvant setting, n</td>
<td>23 (88.5%)</td>
</tr>
<tr>
<td>Neoadjuvant setting, n</td>
<td>3 (11.5%)</td>
</tr>
<tr>
<td>Chemotherapy regimen, n</td>
<td></td>
</tr>
<tr>
<td>EC</td>
<td>14 (53.8%)</td>
</tr>
<tr>
<td>FEC</td>
<td>9 (34.7%)</td>
</tr>
<tr>
<td>EC + Trastuzumab</td>
<td>3 (11.5%)</td>
</tr>
</tbody>
</table>

Aapro et al. conducted a double-blind, randomized phase III study of 300 chemotherapy-naive patients with breast cancer who received anthracycline-based chemotherapy: the first arm received palonosetron and dexamethasone (8 mg) on day 1; the second was given the same day 1 regimen followed by oral dexamethasone (4 mg) twice daily on days 2 and 3. The study showed that this reduced dose of dexamethasone offered similar antiemetic protection to a 3-day dosing schedule (13).

Similarly, in a phase III randomized trial, Celio et al. compared palonosetron and dexamethasone (8 mg) on day 1 versus the same schedule on day 1 followed by dexamethasone (8 mg) given orally on days 2 and 3. A total of 332 patients received moderately emetogenic chemotherapy (MEC) and the CR rate was 67.5% for those administered dexamethasone on day 1 only (14).

Brugnatelli and colleagues demonstrated adequate control of CINV in a phase II, single-center, open-label, non-randomized study. Sixty-eight patients with chemotherapy-naive breast cancer and colorectal cancer were given MEC as adjuvant or first-line treatment. Palonosetron and dexamethasone (8 mg i.v.) were administered on day 1 and CR was observed in 67.6% of patients, while CR during the acute and delayed phases was 75% in each cancer group (15).

Our mono-institutional study showed adequate prevention of acute and delayed emesis following anthracycline-including regimens with palonosetron and a further dose-reduced schedule of dexamethasone. CR (72.4%) was observed overall during chemotherapy (days 1-4) and in 72.4% of all 76 given courses. The use of dexamethasone at 4 mg i.m. from days 1 to 3 did not change glucose levels and confirmed the efficacy and
tolerability of palonosetron. This alternative schedule suggests that the low dose of dexamethasone is efficacious for the control of acute and delayed emesis in MEC. Further investigations are required to confirm these results.

References


