Chemotherapy-induced nausea and vomiting: update and future options

Umberto Pacetti¹
Silvia Ileana Sara Fattoruso¹
Enzo Veltri²

¹Operative Unit of Oncology, A. Fiorini Hospital, Terracina, Italy
²Unit of Medical Oncology, Santa Maria Goretti Hospital, Latina, Italy

Address for correspondence:
Umberto Pacetti
Operative Unit of Oncology, A. Fiorini Hospital
Via Firenze SNC
04019 Terracina (LT), Italy
E-mail: umberto.pacetti@alice.it

Abstract

Even though great progress has been made in the control of chemotherapy-induced nausea and vomiting (CINV), more research is still needed. The use of serotonin 5-HT₃ receptor antagonists (5-HT₃RAs) plus dexamethasone has improved the control of CINV and palonosetron, a second-generation 5-HT₃RA, appears to be the most effective agent in its class. Aprepitant, the first neurokinin 1 receptor antagonist (NK₁RA) has been used effectively as an additive agent to the 5-HT₃RAs while rolapitant and netupitant are being evaluated in phase III clinical trials. This review is an update of the current schedules in preventing CINV and considers possible future strategies.

KEY WORDS: palonosetron and CINV, NEPA, NK 1 receptor antagonists.

Introduction

Chemotherapy-induced nausea and vomiting (CINV) is associated with a significant deterioration in quality of life and may occur any time after administration of chemotherapy: the term ‘acute phase’ refers to nausea and/or vomiting occurring in the first 24 h after chemotherapy while ‘delayed phase’ develop in the period of 1-5 days after chemotherapy (1). CINV can result in serious complications, such as weakness, weight loss, electrolyte imbalance, dehydration or anorexia, decline in behavioural and mental status and wound dehiscence (2). As such, evaluating the safest and efficacious antiemetic regimen remains paramount to ameliorating the outcomes of patients. The use of serotonin 5-HT₃ receptor antagonists (5-HT₃RAs) plus dexamethasone has improved the control of CINV and recent studies have demonstrated some improvement in the control of CINV with the use of new agents: palonosetron, a second-generation 5-HT₃RA; aprepitant, fosaprepitant, netupitant, casopitant, rolapitant, neurokinin 1 receptor antagonists (NK₁RAs) (3-6).

Despite the introduction of more effective antiemetic agents, emesis and nausea remain a significant complication of chemotherapy. The purpose of this review is to update our knowledge about the antiemetic schedules for the prevention and treatment of CINV and to evaluate future strategies.

Methods

We performed an electronic database search of Medline (last search, June 10 2014) and identified phase III and II trials evaluating use of palonosetron and NK₁RAs. Reference lists included meta-analyses, review articles and recent oral sessions from the annual meeting of the American Society of Clinical Oncology (ASCO) 2014. Data of this review obtained from the PubMed database using the following terms: "palonosetron and aprepitant", "NK1 receptor antagonists", "NEPA", "CINV and treatment".

Serotonin 5-HT₃ receptor antagonists

Serotonin receptors exist in the central nervous system and in the gastrointestinal (GI) tract. They appear to act through both the central nervous system and GI tract via the vagus and splanchnic nerves (7, 8). The first-generation 5-HT₃RAs (ondansetron, granisetron, tropisetron, dolasetron, azasetron and ramosetron) are equivalent in efficacy and toxicities when used in the recommended doses, but in 2010 the US FDA announced that the intravenous form of dolasetron should no longer be used to prevent CINV in any patients because of increasing the risk of developing a prolongation of the QT interval, which may potentially precipitate life-threatening ventricular arrhythmias (9-11). The first-generation 5-HT₃RAs have not been as effective against delayed emesis as they are against acute phase and do not add significant efficacy to that obtained by dexamethasone as they are against acute phase and do not add significant efficacy to that obtained by dexamethasone in the delayed phase. A randomized controlled trial showed that the first-generation 5-HT₃RAs were no more effective than prochlorperazine in controlling nausea in the delayed period and a meta-analysis reported that there was...
neither clinical evidence nor considerations of cost-effectiveness to justify using these drugs for the prevention of delayed emesis (12-14).

**Palonosetron: the new generation**

Palonosetron belongs to the second-generation 5-HT₃RAs having a higher potency and a significantly longer half-life. Its binding affinity is almost 30-fold higher than other 5-HT₃RAs and causes internalization of the receptor with prolonged inhibition of its function. A previous meta-analysis included nine randomized controlled trials and showed that palonosetron was statistically superior to the other 5-HT₃RAs in Complete Response (CR) in all three phases and in Complete Control (CC) of the delayed and overall phases. The four most common treatment-associated adverse events of palonosetron are constipation, headache, dizziness, and diarrhea, but in this meta-analysis dizziness, diarrhea, and QTc prolongation were not analyzed (15, 16). Popovic et al. reviewed a total of 16 randomized controlled trials to compare palonosetron to other 5-HT₃RAs in CINV prophylaxis. They identified 2,896 patients randomized to palonosetron and 3,187 patients to other 5-HT₃RAs and found that palonosetron was consistently statistically superior in terms of CR, CC, no emesis and no nausea. The percentage of patients not receiving rescue medication demonstrated superior palonosetron only in the overall phase. Subgroup analyses did not demonstrate a higher degree of benefit of palonosetron relative to other inhibitors between patients received Highly Emetogenic Chemotherapy (HEC) and Moderately Emetogenic Chemotherapy (MEC). In the acute phase, the addition of dexamethasone led to CR, no emesis and no nausea being statistically similar between arms and only CC showing statistical superiority of palonosetron over other 5-HT₃RAs. In the delayed and overall phases all endpoints of the corticosteroids analysis were statistically significant in favor of palonosetron. Palonosetron was significantly safer to other inhibitors in dizziness and mean QTc prolongation; constipation, headache and diarrhea were similar between arms (17). At the moment this is the largest update of previous meta-analyses.

**Neurokinin 1 Receptor Antagonists: the new drugs**

The role of serotonin in the induction of CINV may be particularly relevant in the first 8-16h following the administration of chemotherapy (18). Thus, other mechanisms and neurotransmitters are necessarily involved in the induction of delayed CINV. One of the major factors responsible of delayed CINV is substance P, which is released by sensory nerve endings and plays a key role in transmitting information on pain to the brain; it is involved in several activities and has been shown to play an important role in the pathogenesis of acute and delayed CINV. The biological activities of substance P are mediated by NK1 receptors (19). Aprepitant is an NK₁RA that blocks the emetic effects of substance. When combined with a standard regimen of the corticosteroid dexamethasone and a 5-HT₃RA, aprepitant is effective in the prevention of CINV in patients receiving HEC (20, 21).

The benefit from the addition of aprepitant was shown in three randomized phase III trials in HEC and two randomized phase III trials in MEC. In HEC, the addition of aprepitant (125 mg on day 1, 80 mg on days 2, 3) was compared to intravenous ondansetron 32 mg (on day 1) and oral dexamethasone (12 or 20 mg on days 1 and 8 or 16 mg on days 2, 3). In one of these studies ondansetron was administered orally (16 mg on days 2 to 4). The addition of aprepitant significantly improved the rate of CR and a pronounced benefit was observed in the prevention of delayed emesis, with an absolute increase in the CR rate of 19%, 21% and 11%, respectively (22-24). In MEC, two studies compared the addition of aprepitant to ondansetron plus dexamethasone and significantly improved the prevention of CINV in terms of CR following the first cycle. The benefit of aprepitant was more pronounced in AC-based MEC, where an increase of 16% in the CR was reported compared with the 8.4% in non-AC-based MEC (25, 26). Because of its oral formulation, the administration of aprepitant should be carefully monitored. To address this issue, fosaprepitant was approved for use in clinical practice by FDA and EMA in 2008. It is a water-soluble phosphoryl pro-drug for aprepitant that, when administered intravenously, is converted to aprepitant within 30 minutes. A single dose of intravenous fosaprepitant 150 mg on day 1 of cisplatin chemotherapy was not inferior to a 3-day oral regimen of aprepitant in the prevention of CINV in the 120 h post-chemotherapy (27).

Casopitant competitively binds to the NK₁ receptor, thereby inhibiting NK₁ receptor binding of substance P and blocking the activity of the receptor. Three phase III clinical trials with intravenous and oral casopitant have been completed and two of them demonstrated that casopitant was more effective in the prevention of vomiting than dexamethasone and ondansetron alone in patients with solid malignant tumours receiving cisplatin-based HEC and non-cisplatin-based MEC. There have been no reported serious adverse events related to casopitant and common adverse events (neutropenia, constipation, alopecia, fatigue) occurred with comparable frequency across control and treatment groups (28-31).

Rolapitant, another NK₁RA, is being evaluated in clinical trials. A phase II trial in patients receiving HEC demonstrated that rolapitant improved CR in the acute, delayed and overall period when added to ondansetron and dexamethasone. A recent phase III trial presented at ASCO annual meeting 2014 showed the efficacy of rolapitant administered with granisetron and dexamethasone in 555 cisplatin-naïve subjects treated with HEC. Patients in the rolapitant group had a significantly higher CR rate in the acute, delayed and overall phases compared to granisetron and dexamethasone plus placebo. Moreover, the rolapitant group achieved higher rates of complete protection in both delayed and overall phases (32, 33).

**NEPA: the future**

NEPA is an oral fixed-dose combination of netupitant, a new highly selective NK₁RA and palonosetron. This new
5-HT₃RA inhibits the cross-talk between the 5-HT₃ and NK1 receptors and the combination of palonosetron with netupitant has been shown to work synergistically in enhancing inhibition of the substance P response compared with either antagonist alone (34).

The efficacy of NEPA was evaluated in a recent dose-ranging study and two phase III trials. In the phase II study, 694 patients undergone cisplatin-based therapy for solid tumours, were randomized to evaluate three different oral doses of netupitant (100, 200 and 300 mg) and palonosetron 0.50 mg with oral palonosetron 0.50 mg, all given on day 1. A standard 3-day aprepitant IV ondansedron 32 mg regimen was included as an exploratory arm and all patients received oral dexamethasone on days 1-4. All NEPA doses showed superior overall CR rates compared with palonosetron with the highest NEPA dose (300 mg) studied showing an incremental benefit. NEPA300 was significantly more effective than palonosetron and numerically better than aprepitant and ondansetron for no emesis, no significant nausea and complete protection during the acute, delayed and overall phases. Adverse events were comparable across group and the percent of patients developing electrocardiogram changes was also comparable (35).

In two phase III trials the safety and efficacy of NEPA were evaluated for prevention of CINV following MEC regimens and repeated cycles of chemotherapy, respectively.

In MEC, a single oral dose of NEPA was compared with a single oral dose (0.50 mg) of palonosetron. All patients received oral dexamethasone on day 1. The percentage of CR during the delayed phase was significantly higher in the NEPA group as were the percentages in the overall and acute phases. NEPA was also superior to palonosetron for no emesis, no significant nausea and complete protection. The safety profiles were similar (Fig.1) (36).

In MEC and HEC regimens, a single dose of NEPA given with oral dexamethasone was compared with an oral 3-day aprepitant regimen + palonosetron + dexamethasone over multiple cycles. The overall CR rates (0-120 h) in cycle 1 were superior for NEPA and antiemetic efficacy was maintained over repeated cycles. The incidence and type of adverse events were comparable for both groups (Tab.1) (37).

A phase III study that exclusively evaluated the efficacy and safety of NEPA during repeated MEC cycles has been recently presented at annual meeting of ASCO. All patients received oral dexamethasone (12 mg) and NEPA or dexamethasone (20 mg) and palonosetron on day 1. The superiority of NEPA over palonosetron for overall CR during the first cycle was maintained over multiple administrations of chemotherapy.

---

Table 1- Overview of adverse events.

<table>
<thead>
<tr>
<th>Type of adverse event</th>
<th>NEPA (N=308)</th>
<th>APR+ PALO (N=104)</th>
<th>NEPA (N=308)</th>
<th>APR+PALO (N=104)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cycle 1</td>
<td>Entire multiple cycle study period</td>
<td>Cycle 1</td>
<td>Entire multiple cycle study period</td>
</tr>
<tr>
<td>Any ‘treatment-emergent’ adverse event</td>
<td>199 (64.6%)</td>
<td>64 (61.5%)</td>
<td>265 (86.0%)</td>
<td>95 (91.3%)</td>
</tr>
<tr>
<td>‘Treatment-related’ adverse event</td>
<td>16 (5.2%)</td>
<td>3 (2.9%)</td>
<td>31 (10.1%)</td>
<td>6 (5.8%)</td>
</tr>
<tr>
<td>‘Severe’ treatment-related adverse event</td>
<td>1 (0.3%)</td>
<td>0</td>
<td>1 (0.3%)</td>
<td>0</td>
</tr>
<tr>
<td>‘Serious’ treatment-related adverse event</td>
<td>1 (0.3%)</td>
<td>0</td>
<td>2 (0.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Treatment-related adverse event ‘leading to discontinuation’</td>
<td>1 (0.3%)</td>
<td>0</td>
<td>1 (0.3%)</td>
<td>0</td>
</tr>
<tr>
<td>‘Total deaths’ (all unrelated to study drug)</td>
<td>7 (2.3%)</td>
<td>0</td>
<td>16 (5.2%)</td>
<td>1 (1.0%)</td>
</tr>
</tbody>
</table>

---

Figure 1 - Different complete response between NEPA and palonosetron.

Reviews in Oncology 2014; 2(1):7-12
There was not difference in incidence of adverse events between groups (38).

Discussion

The Multinational Association Supportive Care in Cancer (MASCC) and the European Society for Medical Oncology (ESMO) established guidelines to maximize control of CINV in clinical practice. For the prevention of nausea and vomiting because of HEC, it is recommended the administration of a three-drug regimen containing single dose of aprepitant, 5-HT3RAs and dexamethasone. Palonosetron significantly improved the outcome in delayed phase and is preferred in this regimen (39-41). A combination of dexamethasone and palonosetron is suggested for standard prophylaxis of acute emesis in MEC and patients treated with AC-based chemotherapy should receive a combination of aprepitant, dexamethasone and 5-HT3RAs. To prevent delayed emesis in non-AC-based chemotherapy, dexamethasone should be considered.

To monitor more carefully the administration of aprepitant, its intravenous formulation (fosaprepitant) was approved in clinical practice and seems not inferior in preventing nausea and vomiting. The new NK1RAs appear to have potential for use in the prevention of CINV. Particularly, NEPA showed superior in patients receiving HEC and MEC and provided evidence of excellent emetic control over multiple chemotherapy cycles.

Next trials should evaluate more appropriate doses of dexamethasone in antiemetic regimens because lower doses could be sufficient when administered with 5-HT3RAs/NK1RAs. Phase II-III studies showed an adequate control of CINV with low dose of dexamethasone in HEC and MEC during acute and delayed phase (42-44). In a phase II non-randomized study patients with type 2 diabetes mellitus and those prone to osteoporosis could benefit from a dose-reduced regimen of dexamethasone and palonosetron (45).

The development of new combination strategies with dexamethasone and these innovative drugs could improve quality of life of patients during chemotherapy.

References

Chemotherapy-induced nausea and vomiting: update and future options


