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REVIEW ARTICLE

Prophylactic treatment for delayed chemotherapy-induced nausea and vomiting after non-AC based moderately emetogenic chemotherapy: a systematic review of randomized controlled trials

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Abstract
Purpose Delayed chemotherapy-induced nausea and vomiting (CINV) remains an important adverse effect of moderately emetogenic chemotherapy not containing anthracyclines and cyclophosphamide (non-AC MEC). In this review, we summarize current literature to update recommendations for delayed CINV prophylaxis after non-AC MEC.
Methods We conducted a systematic search in PubMed and conference proceedings from ASCO, ESMO, and MASCC. Included randomized controlled trials (RCTs) aimed to prospectively evaluate the efficacy of two or more antiemetic strategies in the prevention of delayed CINV after the administration of non-AC MEC. At least one of the following endpoints was used: complete response, complete control, no nausea, no vomiting, and/or no use of rescue medication.
Results Our search provided 247 publications. Nine met the predefined criteria. Included RCTs reported outcomes on palonosetron, aprepitant, casopitant, netupitant/palonosetron (NEPA), olanzapine, and megestrol acetate.
Conclusions Superiority of palonosetron over first-generation 5-HT_3 receptor antagonists for the prevention of acute and delayed CINV after non-AC MEC has not been proven. The addition of an NK_1 receptor antagonist to first-generation 5-HT_3 receptor antagonists does not significantly improve the incidence of delayed CINV after non-AC MEC. The efficacy of a single-day regimen of dexamethasone with palonosetron is non-inferior to multiday dexamethasone. NEPA, olanzapine, and megestrol acetate show highly effective complete response (CR) rates.

Keywords Antiemetics · Delayed CINV · Moderately emetogenic chemotherapy

Introduction

Delayed chemotherapy-induced nausea and vomiting (CINV), defined as nausea and vomiting occurring more than 24 h after completion of chemotherapy, remains an important and common adverse event complicating cancer treatment. Delayed CINV significantly interferes with patient's quality of life (QOL) and daily functioning [1, 2]. Incidence and severity of CINV are affected by patient- and treatment-related factors. Characteristics associated with a higher risk include female sex, anxiety, and poor control with previous chemotherapy [3, 4]. Delayed CINV is influenced by the effectiveness of control of the acute phase of CINV, as well as the intrinsic emetogenicity of the drug. The risk of delayed CINV has been studied best in chemotherapy regimens containing high-dose cisplatin or anthracyclines and cyclophosphamide (AC) combinations. However, delayed CINV is also associated with moderately emetogenic chemotherapy (non-AC MEC) regimens [5–10]. Non-AC MEC consists of a broad range of chemotherapeutic agents, with emetogenic potentials of 30 to 90 %; agents like oxaliplatin and irinotecan have an

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emetogenic potential in the lower part of this range, as opposed to carboplatin, which is at the high end [11, 12].

In 2013, the Multinational Association for Supportive Care in Cancer (MASCC) and the European Society of Medical Oncology (ESMO) last updated their guidelines for the management of CINV in adults [13]. In 2011, the American Society of Clinical Oncology (ASCO) published the last updated clinical practice guideline for antiemetics in oncology [14]. All guidelines recommend palonosetron combined with dexamethasone for the prevention of acute CINV following non-AC MEC, with multiday oral dexamethasone as the preferred treatment for the prevention of delayed CINV (level of evidence IIb). These recommendations are based however on phase III trials, which did not evaluate the combination of palonosetron and dexamethasone in MEC, but only in highly emetogenic chemotherapy (HEC) and AC chemotherapy [15, 16]. Also, patients in the aforementioned trials did not receive optimal antiemetic treatment with NK_1 receptor antagonists, as recommended for HEC and AC chemotherapy, which may have influenced the results.

Despite the recommended combination of palonosetron and multiday dexamethasone, many patients still experience delayed CINV following non-AC MEC. In a small observational trial with colorectal cancer patients, palonosetron and dexamethasone failed to provide both complete response (CR) and complete control (CC) in 15 % of the patients in the delayed phase [17]. In another phase III trial with palonosetron and dexamethasone administered for 3 days, almost 25 % of the patients did not achieve CR in the delayed phase [18]. Further evidence on the efficacy of new strategies to prevent delayed CINV after non-AC MEC is therefore needed. This systematic review aims to provide a comprehensive assessment of recently performed randomized controlled trials (RCTs) on this specific topic.

Methods

Search strategy

We conducted a systematic search in PubMed and conference proceedings of ASCO, ESMO, and MASCC in August 2014. For PubMed, the following syntax was applied: “chemotherapy-induced nausea and vomiting [tiab]” OR “CINV [tiab]” OR “emesis [tiab]” OR “delayed nausea [tiab]” OR “moderately emetogenic [tiab]” OR “MEC [tiab]”, with limits: clinical trial, full text, English, humans, adult, and date from January 1st 2009 to July 31st 2014. An electronic search was undertaken of conference proceedings of ASCO, ESMO, and MASCC from January 1st 2009 to July 31st 2014.

Selection criteria

Potentially relevant studies retrieved by the PubMed and conference proceedings searches were independently reviewed for eligibility by two investigators (M.V.D.V. and E.C.W.N.). Any disagreement between the reviewers was resolved by re-examination and subsequent discussion to reach a consensus. Unpublished or retrospective studies were not considered eligible. Levels of evidence were not used to assess the value of each publication selected for inclusion. The following criteria for inclusion were applied: (a) The study aimed to prospectively evaluate the efficacy of two or more antiemetic strategies in the prevention of delayed CINV after the administration of moderately emetogenic chemotherapy not containing anthracyclines and cyclophosphamide (non-AC MEC). (b) At least one of the following endpoints was used in the study: (1) complete response, (2) complete control, (3) no nausea, (4) no vomiting, or (5) no use of rescue medication. Studies on patients receiving chemotherapy with mixed emetogenicity (HEC and/or AC and/or non-AC MEC) were included only if subgroup analysis (pre-planned or ad hoc) of the non-AC MEC subgroup was performed. When data on AC and non-AC MEC were combined, it was arbitrarily decided to include studies in which the percentage of patients receiving AC was less than 50 % in the subgroup analysis. Both RCTs in which the antiemetic therapies only differed beyond day 1, and RCTs in which there was a difference starting at day 1 were included.

Data extraction

Extracted items were study design, number of patients included, number of patients receiving non-AC MEC, tumor types, emetogenic level of assessed chemotherapeutic agents, primary efficacy endpoints, intervention, and reported results. Because of the heterogeneity in study designs, risk of bias, and variety in patient populations, conducting a meta-analysis was not possible.

Results

Number of studies meeting selection criteria

Using the PubMed syntax and aforementioned limits, 247 potentially relevant studies were identified. Figure S1 (available at the *Journal of Supportive Care in Cancer* online) depicts the subsequent stepwise selection of nine eligible studies. Searching conference proceedings of ASCO, ESMO, and MASCC did not provide additional eligible studies.

Characteristics eligible studies

Our search provided nine studies which met the selection criteria [18–26]. Mean sample size was 320 patients. Mean number of patients receiving non-AC MEC was 230. All but three studies assess patients with various tumor types. Most studies assessed antiemetics in patients receiving a broad range of chemotherapy regimens, including HEC, AC, and MEC regimens; three studies assessed non-AC MEC only. Most studies were double-blinded, including one phase II trial. Three had a crossover study design. Two were non-inferiority trials. Palonosetron was assessed in three studies, including one evaluating a dexamethasone-sparing regimen. NK_1 receptor antagonists were assessed in three studies, including one evaluating casopitant. Although casopitant was discontinued for further development, we included data from this RCT because they provide evidence to clarify the usage of NK_1 receptor antagonists for non-AC MEC. Other antiemetics assessed were netupitant/palonosetron (NEPA), olanzapine, and megestrol acetate, each in one study. CR (defined as "no vomiting," and/or "no use of rescue antiemetics") in the acute, delayed, and overall phases was the primary efficacy endpoint in the majority of the studies included. Study details are summarized in Table 1.

Palonosetron

An open-label, crossover trial was designed to evaluate the efficacy of palonosetron compared with ondansetron [19]. This study included 30 patients with head and neck cancer. All patients received the same non-AC MEC regimen docetaxel 60 mg/m^2, carboplatin 300 mg/m^2, and 5-fluorouracil 600 mg/m^2. Previous exposure to chemotherapy is unknown. Corticosteroids were administered to all patients on day 1. CR (defined as no vomiting) and intensity of nausea in the acute, delayed, and overall phases were the primary efficacy endpoints in this study. There were no significant differences in CR rates in all phases (palonosetron vs. ondansetron: acute phase 83.3 vs. 80 %; delayed phase 76.6 vs. 66.7 %; overall phase 66.7 vs. 46.7 %; p values not provided). Differences in control of nausea were also not statistically significant during all phases.

In a multicenter, double-blind, non-inferiority, crossover trial, 144 patients with a broad range of tumor types receiving HEC (cisplatin), AC, or non-AC MEC were randomized to palonosetron in cycle 1, and then switched to granisetron in cycle 2 or vice versa [20]. Both chemotherapy naïve and non-naïve patients were included. Corticosteroids were not allowed. The primary efficacy endpoint in this study was the proportion of patients with CR (no vomiting) during the acute, delayed, and overall phases. One hundred and eight patients (75 %) received AC or non-AC MEC (63 % of patients in this subgroup). One hundred and twenty-two patients received two cycles of chemotherapy. Data of both cycles were pooled. In the mixed AC/non-AC subgroup, differences in CR rates between palonosetron and granisetron were not significant; in the acute phase 72.16 vs. 67.65 %; in the delayed phase 67.01 vs. 59.80 %; in the overall phase 58.76 vs. 52.9 %, respectively. p values not provided.

Dexamethasone-reducing study

A multicenter, open-label, non-inferiority study published in 2011 was designed to evaluate the efficacy of palonosetron plus single-day dexamethasone compared with multiday dexamethasone. This study included 332 patients receiving AC or non-AC MEC, mainly oxaliplatin-, irinotecan-, and carboplatin-based regimens [18]. All patients were chemotherapy naïve. CR (defined as no vomiting, no use of rescue medication) during the overall phase was the primary outcome measure. In the overall population, differences in CR rates during the overall phase were significant (67.5 % for single-day dexamethasone and 71.1 % for dexamethasone on days 1–3; difference, 95 % CI −3.6 % (−13.5 to 6.3)). In the non-AC MEC subgroup analysis, there were no significant differences in CR rates between the single-day and multiday dexamethasone groups (in the acute phase, 88.3 vs. 87.0 %, respectively (difference, 95 % CI 1.3 (−7.6 to 10.2)); in the delayed phase, 71.2 vs. 76.0 %, respectively (difference, 95 % CI −4.8 (−16.7 to 7))).

NK_1 receptor antagonists

In a multicenter, double-blind study by Rapoport et al., 848 patients receiving AC and non-AC MEC for a broad range of tumors were randomized to compare the efficacy of an oral three-drug regimen of aprepitant, ondansetron, and dexamethasone to an oral control regimen of ondansetron and dexamethasone [21]. Fifty-two percent of the patients were given non-AC-based MEC, including oxaliplatin, carboplatin, ifosfamide, and irinotecan. All patients were chemotherapy naïve. The primary efficacy endpoint of the study was the proportion of patients reporting no vomiting during the overall phase. In the overall population, a significantly higher proportion of patients on aprepitant reported no vomiting in the overall phase compared to the control group (76.2 vs. 62.1 %, respectively, $p<0.001$). In the post hoc analysis of the non-AC MEC subgroup, statistically more patients in the aprepitant group compared to the control group reported no vomiting; in the acute phase, 96.5 vs. 91.6 %, respectively, $p<0.05$; in the delayed phase, 84.5 vs. 73.9 %, respectively, $p<0.05$; in the overall phase, 83.2 vs. 71.3 %, respectively, $p<0.05$.

In a double-blind, parallel group study by Hesketh et al., enrolling 707 patients receiving non-AC MEC (oxaliplatin) for colorectal cancer, the efficacy of single-dose casopitant

Table 1 Characteristics of randomized controlled trials

First author, year	No. pts.	No. pts. with non-AC	Tumor types	Chemotherapy; level of emetogenicity	Study design	Primary efficacy endpoint(s)	Intervention	Results
Palonosetron								
Kaushal, 2010 [19]	30	30	Head and neck	Docetaxel, carboplatin, 5-FU; non-AC MEC	Randomized, crossover	CR (no vomiting) and intensity of nausea, in acute, delayed, and overall phases	Palonosetron vs. ondansetron	NS
Tian, 2011 [20]	144	108[a]	Various	Various; HEC, AC, non-AC MEC	Double-blind, non-inferiority, crossover	CR acute	Palonosetron vs. granisetron	Palonosetron not inferior
Dexamethasone-sparing regimens								
Celio, 2011 [18]	332	215	Various, mainly breast and colorectal	Various; AC, non-AC MEC	Open-label, non-inferiority, parallel	CR overall phase	Palonosetron+dexa d 1 vs. Palonosetron+ dexa d 1–3	Palonosetron d 1 not inferior
NK_1 receptor antagonists								
Rapoport, 2009 [21]	848	444	Various	Various; AC, non-AC MEC	Double-blind, parallel	No vomiting overall phase	Aprepitant vs. ondansetron	Aprepitant superior
Hesketh, 2012 [22]	707	707	Colorectal	Oxaliplatin; non-AC MEC	Double-blind, parallel	CR overall	Casopitant vs. placebo	NS
Tanioka, 2013 [23]	91	91	Gynecological	Carboplatin; non-AC MEC	Double-blind, parallel, phase II	CR overall	Aprepitant vs. placebo	NS
NEPA								
Gralla, 2014 [24]	412	312	Various	Various; HEC, non-AC MEC	Double-blind, parallel	CR acute, delayed, overall	NEPA vs. aprepitant+ palonosetron	NS
Olanzapine								
Tan, 2009 [25]	229	121[b]	Various	Various; HEC, AC, non-AC MEC	Open-label, parallel	CR acute, delayed, overall	Olanzapine d 1–5+dexa d 1 vs. dexa d 1–5	Olanzapine superior
Megestrol acetate								
Zang, 2011 [26]	100	44	Various	Various; HEC, non-AC MEC	Single-blind, crossover	CR acute, delayed, overall	Megestrol acetate vs. placebo	Megestrol acetate superior

HEC highly emetogenic chemotherapy, *AC* anthracycline/cyclophosphamide combination, *non-AC MEC* moderately emetogenic chemotherapy not containing anthracyclines and cyclophosphamide, *CR* complete response, *NS* non-significance, *dexa* dexamethasone, *d* day, *no.* number, *pts* patients

[a] Combined AC and non-AC (non-AC 63 %)

[b] Combined AC and non-AC (non-AC 55 %)

was compared to placebo. All patients received ondansetron on days 1–3 plus dexamethasone on day 1 and were chemotherapy naïve [22]. The primary endpoint in this study was the percentage of patients achieving CR (defined as no vomiting, no use of rescue medication) during the overall phase. There were no significant differences between both groups; 86 % of the patients in the casopitant group vs. 85 % in the placebo group achieved CR (p=0.7273). There were also no significant differences between the casopitant and placebo group in the acute phase (97 vs. 96 %, respectively, p=0.4771) and in the delayed phase (86 vs. 85 %, respectively, p=0.7273). There was also no significant difference in severity of nausea observed between casopitant and placebo in all phases.

Ninety-one female patients who were younger than 70 years, and received carboplatin-based chemotherapy for gynecological tumors, were randomized to aprepitant or placebo in a multicenter, double-blind, phase II trial [23]. All patients received granisetron and multiday corticosteroids. Previous exposure to chemotherapy is unknown. The primary endpoint in the study was CR (no vomiting, no rescue medication) during the overall phase. CR rates were not significantly different between aprepitant and placebo in the overall phase (62 vs. 52 %, respectively, p=0.33). There were also no significant differences in CR rates during the acute and delayed phases between aprepitant and placebo (98 vs. 96 %, respectively, and 62 vs. 52 %, respectively).

NEPA, a fixed-dose combination of netupitant and palonosetron

In a multicenter, double-blind study by Gralla et al., the efficacy of a single dose of NEPA (oral fixed-dose combination of 300 mg netupitant and 0.50 mg palonosetron) was compared to oral aprepitant plus oral palonosetron 0.50 mg, in 412 patients treated with either HEC or non-AC MEC regimens for a broad range of tumors [24]. Seventy-six percent of the patients received non-AC MEC, mainly carboplatin- and oxaliplatin-based chemotherapy. In this study, the dose/schedule of oral dexamethasone was open label and based on the emetogenicity of the chemotherapeutic regimen. All patients were chemotherapy naïve. The study was not only designed primarily to assess the safety of NEPA, but also assessed the efficacy of this antiemetic drug. Overall incidence, type, and frequency of adverse events were comparable between the treatment groups. In the overall population, CR rates (no vomiting, no use of rescue medication) in the overall phase were similar in cycle 1 (81 % in the NEPA group vs. 76 % in the control arm). The reported control of nausea was comparable in both groups: 84–92 % across cycles for NEPA and 81–87 % for the control group. For the non-AC MEC subgroup, CR rates across cycles were also comparable between the treatment groups: 80–93 % in the NEPA group and 82–89 % in the control group.

Olanzapine

In 229 patients with a broad range of tumors, the efficacy of olanzapine was compared to the 5-HT_3 receptor antagonist azasetron in an open-label trial by Tan et al. [25]. Patients receiving HEC, AC, or non-AC MEC were randomized to olanzapine 10 mg days 1–5 plus azasetron 10 mg i.v. and dexamethasone 10 mg i.v. on day 1, or to the control group with azasetron 10 mg i.v. on day 1 plus dexamethasone 10 mg i.v. days 1–5. Both chemotherapy-naïve and non-naïve patients were included. Fifty-six percent of all randomized patients received AC or non-AC MEC. In this mixed subgroup, 55 % of the patients received non-AC MEC, mainly oxaliplatin-based chemotherapy. The primary endpoint in this study was CR (no nausea and vomiting, no use of rescue medication) during the acute, delayed, and overall phases. In the overall population, CR rates in the acute phase were very high (>95 %) and did not significantly differ between olanzapine and 5-day dexamethasone in both the HEC and combined AC and non-AC MEC subgroups. In the combined subgroup, CR rates in the delayed phase were 83 % for the olanzapine group vs. 58 % for the control group (p<0.05); in the overall phase, 83 and 56 %, respectively (p<0.05).

Megestrol acetate

One hundred patients with gastrointestinal or lung cancer, who were treated with HEC or non-AC MEC (mainly oxaliplatin- and irinotecan-based chemotherapy), were randomized in a single-blind, crossover trial published in 2011, to receive either oral megestrol acetate 320 mg or placebo [26]. Corticosteroids were not allowed in this study. Information on previous treatment with chemotherapy was not provided. CR rates in the acute, delayed, and overall phases were primary endpoints. In the non-AC MEC subgroup (44 % of all patients), CR rates were significantly higher in the megestrol acetate group: in the overall phase, 50 vs. 27.3 %, respectively (p=0.002); in the acute phase, 72.7 vs. 59.1 %, respectively (p=0.146); and in the delayed phase, 52.3 vs. 25.0 % (p=0.000), respectively.

Discussion

This review focuses on recent RCTs assessing prophylactic antiemetic treatment for delayed CINV following non-AC MEC. Results from the included trials show a diversity of antiemetic agents assessed. Because of heterogeneity in chosen endpoints, including populations, chemotherapy regimens, and tumor types, comparison of data from these studies is limited. There are, however, several findings of interest. We identified two trials comparing the efficacy of palonosetron to first-generation 5-HT_3 receptor antagonists. Both studies

suggest that palonosetron is equally effective as first-generation 5-HT_3 receptor antagonists for the prevention of acute and delayed CINV after non-AC MEC. This conclusion is consistent with results from recently performed study by Roscoe et al. [27]. They found that in patients treated with chemotherapy with mixed emetogenicity, including non-AC MEC, palonosetron was not more effective than granisetron in rates of average delayed nausea, which was the primary endpoint in this study, when both were combined with single-day dexamethasone and the dopamine (D_2) receptor antagonist prochlorperazine. Because no non-AC MEC subgroup analysis was performed, this study did not meet selection criteria for inclusion in our review. On the other hand, the conclusions of both studies included in our review are at variance with results from a recently performed systematic review and meta-analysis by Popovic et al. that showed that palonosetron was superior to first-generation 5-HT_3 receptor antagonists in preventing acute and delayed CINV [28]. Data from AC and non-AC MEC subgroups were pooled; therefore, this meta-analysis does not specifically address the efficacy of palonosetron for delayed CINV prophylaxis following non-AC MEC.

Obviously, the two included studies regarding palonosetron have some limitations. Both have a crossover design, which causes a considerable risk of bias, including the possibility of a "carry over" of treatment effect from one chemotherapy cycle to the next. The investigators have minimized this risk by pooling data from cycles 1 and 2. Moreover, the total number of included patients on non-AC MEC regimens was only 138. Also, multiday dexamethasone for the prevention of delayed CINV was not allowed in both trials, which is not consistent with current guideline recommendations. This could have influenced the outcome measures used in these studies. Furthermore, CR in the delayed phase was not a primary but secondary endpoint in the largest study. It is doubtful whether this trial was powered sufficiently to detect a difference in both endpoints. Considering this, we conclude that at present, there is still insufficient data to decide whether palonosetron is the preferred 5-HT_3 receptor antagonist following non-AC MEC.

As mentioned before, current guidelines recommend the use of multiday dexamethasone to prevent delayed CINV after non-AC MEC. Dexamethasone use is often accompanied by unpleasant side effects. Reduction of dexamethasone exposure, without a decrease in efficacy, could be beneficial for patients. One study we included in our review reported that the efficacy of a single-day regimen of palonosetron and dexamethasone is non-inferior to palonosetron and multiday dexamethasone in the acute, delayed, and overall phases following non-AC MEC. This evidence may be of particular benefit to patients undergoing multiple cycles of therapy when palonosetron is prescribed and where the long-term side effects of dexamethasone can be reduced.

While the major guidelines do not recommend the use of an NK_1 receptor antagonist for non-AC MEC, there is some evidence that adding aprepitant may improve control of vomiting. Results from the study by Rapoport et al. show that a significantly higher proportion of patients on aprepitant reported the primary outcome of no vomiting during all phases. This study, however, has some limitations. For example, non-AC MEC subgroup analysis was not predefined. Furthermore, multiday ondansetron was used as an active control arm for delayed CINV prophylaxis, which is not justified anymore by clinical evidence [29]. Data from two other included studies assessing NK_1 receptor antagonists are in contrast with the study by Rapoport et al. Both studies were well-designed and assessed the additional effect of NK_1 receptor antagonists to first-generation 5-HT_3 receptor antagonists in homogeneous patient populations with clearly defined tumor types, treated with oxaliplatin- or carboplatin-based chemotherapy. Adding NK_1 receptor antagonists did not improve CR rates during the acute and delayed phase. Therefore, we conclude that so far no convincing evidence exists indicating benefits from adding NK_1 receptor antagonists to standard prophylactic antiemetic treatment following non-AC MEC.

Some phase II studies suggested that adding a NK_1 receptor antagonist to palonosetron and dexamethasone causes high CR rates in patients undergoing HEC or non-AC MEC [30, 31]. CR rates of more than 95 and 85 % could be achieved during the acute and delayed phase, respectively, for patients treated with carboplatin-based chemotherapy. This led to the drug development of NEPA, an oral fixed-dose combination of netupitant, which is a highly selective NK_1 receptor antagonist, and palonosetron. We included the study by Gralla et al., which concluded that this combination drug was safe, well tolerated, and highly effective, when compared to oral 3-day aprepitant and palonosetron, and when both treatment groups are combined with dexamethasone [24]. Because this study was designed primarily to assess the safety of NEPA, we believe that future RCTs should be performed to investigate the efficacy of NEPA in clearly predefined AC and non-AC MEC subgroups.

New anti-CINV regimens for non-AC MEC are evolving. Recently, it was noticed that olanzapine, an atypical antipsychotic, combined with a single dose of dexamethasone and palonosetron was highly effective at controlling acute and delayed CINV in patients receiving HEC [32]. Tan et al. found highly significant CR rates for delayed CINV prophylaxis following non-AC MEC with multiday olanzapine compared to multiday dexamethasone [25]. Consequently, olanzapine could combine reduction of dexamethasone exposure with improved efficacy. This study has some limitations, however, like its open-label design, which could have influenced outcome measures. Moreover, AC and non-AC regimens were taken together in the subgroup analysis. Future studies in clearly defined non-AC MEC subgroups should assess

whether the use of olanzapine results in better CR rates for delayed CINV after non-AC MEC.

The antiemetic potential of megestrol acetate was assessed in one trial in a small population, receiving chemotherapy with mixed emetogenicity [26]. The authors reported highly significant CR rates for non-AC MEC-treated patients, when megestrol acetate was compared to placebo. All patients received granisetron and metoclopramide, but corticosteroids were not allowed. Subgroup analysis for MEC contained both AC and non-AC regimens, which could influence the results. Megestrol acetate should be compared in future trials with standard antiemetics.

There are some limitations of this review. Data of the included RCTs could not be synthesized because of the heterogeneity of antiemetic regimens, patient populations, and variance of primary outcomes. AC and non-AC MEC were often combined in subgroup analyses, making it hard to draw firm conclusions for non-AC MEC regimens.

We conclude that high-level evidence for optimal prophylaxis of delayed CINV after non-AC MEC is lacking. We believe that further research is essential to improve antiemetic treatment efficacy and outcome while treatment (dexamethasone)-related toxicities are minimized and acceptable.

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