Efficacy of neurokinin-1 receptor antagonists in the prevention of Chemotherapy-Induced Nausea and Vomiting in patients receiving carboplatin-based chemotherapy: a systematic review and meta-analysis.

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Abstract

According to current ESMO – MASCC guidelines, a combination of a neurokinin-1 receptor antagonist (NK1RA), dexamethasone and a 5-HT3 receptor antagonist (5-HT3RA) is recommended to prevent carboplatin-induced emesis, albeit with moderate level of confidence and not unanimous consensus. We performed a meta-analysis of randomized trials (RCTs) comparing NK1RA + dexamethasone + 5-HT3RA vs. dexamethasone + 5-HT3RA in patients receiving the first cycle of carboplatin-based chemotherapy. Primary outcome was complete response (CR), defined as no emesis and no use of rescue medication. 9 trials were eligible, and data of CR were available from 8 trials (1598 patients). Addition of NK1RA improves CR in all phases: acute phase, 94.5% vs. 90.1%; delayed phase, 76.4% vs. 61.7%; overall period, 75.3% vs. 60.4%. There was no significant heterogeneity among trials. In patients receiving carboplatin-based chemotherapy, the addition of NK1RA to dexamethasone and 5-HT3RA is associated with a statistically significant and clinically relevant improvement in CR.

Key words: chemotherapy-induced nausea and vomiting, carboplatin, NK1 receptor antagonist, aprepitant, fosaprepitant, rolapitant, systematic review, meta-analysis

1. Introduction

Nausea and vomiting are common adverse events in cancer patients receiving chemotherapy [1,2]. Chemotherapy-induced nausea and vomiting (CINV) can significantly affect health-related quality of life (QoL) of cancer patients and can impair compliance with treatments [3,4]. For these reasons, a correct management of CINV is essential. According to guidelines, all antineoplastic agents are classified, based on their emetogenic potential, on a 4-group scale: high (emetic risk >90%), moderate (30%–90%), low (10%–30%), and minimal (<10%) emetogenic chemotherapy [4]. For each category, guidelines recommend different strategies to prevent CINV: a triple drug strategy with 5-hydroxytryptamine type 3 (5-HT3) receptor antagonists (RAs) plus dexamethasone plus Neurokinin-1 (NK-1) RAs is currently recommended in highly emetogenic chemotherapy (HEC) (such as cisplatin-based treatment or combination of anthracyclines and cyclophosphamide in breast cancer patients) to prevent acute and delayed nausea and vomiting [5,6]. In patients receiving moderately emetogenic chemotherapy (MEC) such as oxaliplatin and irinotecan, only 5-HT3RA and dexamethasone are recommended. Instead, for carboplatin, the latest ESMO-MASCC guidelines recommend a different prophylaxis compared to other MEC, consisting in a triple combination of 5-HT3RA plus dexamethasone plus NK-1RA [5]. However, the level of confidence was moderate, and the consensus reached among panelists was not unanimous.

To better define the value of NK-1RAs addition in the prevention of emesis for patients receiving carboplatin-based chemotherapy, we conducted a systematic review and a literature-based meta-analysis of all randomized trials (RCTs) published to date.

2. Methods

This systematic review and meta-analysis was conducted and reported according to PRISMA guidelines [7]. Full protocol of the review is available on request from the corresponding author.

The systematic review was performed in January 2017 and updated in June 2017, in order to identify all RCTs comparing NK1RA + dexamethasone + 5-HT3RA vs. dexamethasone + 5-HT3RA in patients receiving the first cycle of carboplatin-based chemotherapy. PubMed search was based on the following key-words: *"aprepitant" OR "fosaprepitant" OR "netupitant" OR "rolapitant") AND "carboplatin".* References of the selected articles were also checked to identify further eligible trials. Furthermore, the proceedings of the main International meetings (American Society of Clinical Oncology, European Society of Medical Oncology, Multinational Association of Supportive Care in Cancer), were searched from 2010 onwards.

Both RCTs including only patients receiving carboplatin, and subgroup analyses of patients receiving carboplatin within RCTs including various MEC regimens, were identified as eligible for the meta-analysis.

Primary outcome was complete response (CR), defined as no emesis and no use of rescue medication. Secondary outcome was the absence of nausea. CR and no nausea were measured in day 1 (acute phase), days 2-5 (delayed phase) and days 1-5 (overall period).

Data were extracted independently by two authors (MDM, MM). After data were abstracted from each study, meta-analysis was performed using Review Manager (RevMan 5.3) software. Given that both complete response and no nausea are dichotomous outcomes, cumulative rates were calculated summing up the results obtained in each study. For both experimental and control arm, the number of patients obtaining complete response and the number of patients obtaining no nausea for each phase (acute,

delayed, overall) was extracted from each article, and input in RevMan as number of events (numerator), while the total number of patients assigned to the arm was used as denominator.

Data were pooled using Odds Ratios for complete response and no nausea. A random effects model was applied. Statistical heterogeneity between studies was examined using the χ^2 test and the I^2 statistic.

3. Results

Out of 180 records, 173 were excluded and 7 trials were identified as potentially eligible (**Figure 1**) [8-14] . In addition, 2 trials were found in the proceedings of meetings [15,16], for a total of 9 trials potentially eligible. More specifically, 7 trials tested the role of aprepitant, 1 fosaprepitant and 1 rolapitant; 6 trials were RCTs including only patients receiving carboplatin, and 3 were subgroup analyses of patients receiving carboplatin within RCTs including various MEC regimens.

Characteristics of the trials included, in terms of study phase, label (open label vs. blinded), randomization procedure, NK1RA used, chemotherapy and antiemetic regimens, are detailed in **Table 1**. One of the trials [8] also included 1 patient who did not receive carboplatin-based treatment, but 5-fluorouracil + leucovorin + irinotecan. However, considering that all other patients received carboplatin, the trial was considered eligible.

Data of CR were available in 8 trials [8-15], including 1598 patients: 793 patients were assigned to experimental treatment including NK1RA, dexamethasone and 5HT3RA, and 805 patients were assigned to control treatment with dexamethasone and 5HT3RA alone. Details of CR in each trial arm are reported in **Table 2**.

Results of the meta-analysis for primary endpoint (CR) are shown in **Figure 2** and **Figure 3**. In the acute phase, the CR rate was significantly higher with addition of NK1RA: namely, 94.5% vs 90.1% (Odds Ratio 1.75, 95%CI 1.19-2.59, p=0.005). In the delayed phase, the CR rate was significantly higher with addition of NK1RA: 76.4% vs 61.7% (Odds Ratio 2.04, 95%CI 1.64-2.55, p<0.00001). Finally, in the overall period (0-120 h), the CR rate was significantly higher with the addition of NK1 RA: 75.3% vs 60.4% (Odds Ratio 2.04, 95%CI 1.64-2.54, p<0.00001). There was no significant heterogeneity among trials, across all the analyses.

Sensitivity analyses were conducted, excluding open-label trials, and excluding subgroup analyses of RCT including various chemotherapy regimens. These sensitivity

analyses produced similar results. More specifically, the sensitivity analysis excluding open-label trial was based on 4 trials (1302 patients). The CR rate was significantly higher with the addition of NK1RA: namely, 93.8% vs 90.7% (Odds Ratio 1.54, 95%CI 1.01-2.33, p=0.04) in the acute phase; 74.9% vs 60.4% (Odds Ratio 2.01, 95%CI 1.58-2.55, p<0.00001) in the delayed phase; 73.6% vs 59.4% (Odds Ratio 1.97, 95%CI 1.55-2.50, p<0.00001) in the overall period (0-120h), without significant heterogeneity among trials. The sensitivity analysis excluding subgroup analyses was based on 6 trials (684 patients). The CR rate was significantly higher with the addition of NK1RA: namely, 95.6% vs 89.7% (Odds Ratio 2.41, 95%CI 1.23-4.71, p=0.01) in the acute phase; 71.8% vs 57.6% (Odds Ratio 1.89, 95%CI 1.36-2.62, p=0.0002) in the delayed phase; 70.6% vs 55.6% (Odds Ratio 1.96, 95%CI 1.43-2.71, p<0.0001) in the overall period (0-120h), without significant heterogeneity among trials.

Data of the secondary endpoint (no nausea) were available in 6 trials [8,9,11-14], including 1005 patients, for the overall period, and in 5 trials [9,11-14], including 914 patients, for the acute and delayed phases. Results of the meta-analysis for no nausea are shown in **Figure 4**. In the acute phase, the rate of no nausea was not significantly different between treatment groups: namely, 82.7% vs 78.7% (Odds Ratio 1.32, 95%CI 0.75-2.33, p=0.33). In the delayed phase, the rate of no nausea was significantly higher with addition of NK1RA: 56.0% vs 44.2% (Odds Ratio 1.93, 95%CI 1.14-3.25, p=0.01). Finally, in the overall period (0-120 h), the rate of no nausea was significantly higher with the addition of NK1 RA: 54.5% vs 42.6% (Odds Ratio 1.77, 95%CI 1.19-2.63, p=0.004). For this endpoint, heterogeneity among trials was higher than complete response analysis.

4. Discussion

In this meta-analysis, we collected the results of all RCTs comparing antiemetic prophylaxis based on the combination of 5-HT3RA plus dexamethasone with the same combination implemented with a NK1RA, in patients undergoing carboplatin-based chemotherapy. Through the comparison of complete response rates (defined as no episodes of emesis and no need for rescue medications), we demonstrated that the addition of a NK1RA significantly increases the rate of success in the control of CINV after the first cycle of chemotherapy. Notably, this benefit was evident in the acute phase (absolute difference of about 4%), and was even higher in the delayed phase (absolute difference of about 14%, which compares favorably with the benefit obtained from the triple combination in highly emetogenic chemotherapy).

The combination of dexamethasone and 5-HT3RA has historically been indicated as standard antiemetic prophylaxis for patients receiving carboplatin-based regimens [6]. However, the efficacy of a two-drug prophylaxis has been reported to be suboptimal, especially in the delayed phase [17].

The 2016 edition of MASCC/ESMO Consensus Guidelines for the prevention of CINV recommends the association of NK1RA, dexamethasone and 5-HT3RA for carboplatin-based chemotherapy, even if the level of confidence and consensus among panelists was moderate, due to the limitations of clinical studies available [5].

The quality and characteristics of trials included in our meta-analysis were heterogeneous. However, two sensitivity analyses (performed exclusively on double-blind trials and excluding subgroup analyses of RCTs generically including MEC) confirmed the main result for the primary endpoint. Furthermore, the meta-analysis did not show significant heterogeneity among trials for complete response, neither for the acute nor for the delayed phase.

Our meta-analysis supports the use of a three-drug prophylaxis for patients undergoing carboplatin-based chemotherapy. As for the acute phase, the absolute CR difference in favor of the addition of NK1RA is lower than what is obtained in HEC, and below 10%, which is considered by MASCC as a threshold to be clinically meaningful [5]. However, given that the proportion of complete responders was already higher than 90% in the control arm, the 10% threshold for clinical relevance of this improvement cannot be properly applied. As for the delayed and overall phases, the difference is instead larger than the 10% threshold. Most recently, also the NCCN guidelines updated the emetogenic status of carboplatin: in the 2.2017 edition, carboplatin-based regimens (when administered at area under the curve ≥4 mg/mL per minute) was escalated to HEC, where a triple drug regimen should be preferred [18]. Similarly, the recent update of the ASCO clinical practice guidelines recommend the addition of a NK1RA for adults who receive carboplatin area under the curve ≥4 mg/mL per minute [19].

In the absence of direct comparisons specifically conducted in patients receiving carboplatin, no recommendation for a specific NK1RA can be made. Trials available were conducted with aprepitant, fosaprepitant and rolapitant, while no trial is available testing the addition of netupitant to dexamethasone and 5HT3RA. However, based on a *post hoc* analysis, which indirectly compared netupitant with aprepitant, the recommendation can be reasonably extended also to netupitant [20]. Furthermore, although limited by indirectness, a randomized trial conducted in patients receiving highly emetogenic chemotherapy showed that a triple antiemetic prophylaxis including netupitant was non-inferior compared to a triple prophylaxis including aprepitant, with very similar overall CR rates and a similar safety profile [21]. However, because no comparative studies are available to assess variations in efficacy between different NK1RAs in patients receiving carboplatin, the different drug metabolism, the administration route as well as the costs should all be elements considered when making a choice.

One limitation of this meta-analysis is the absence of individual patient data. Those would have allowed the description of the interaction between treatment efficacy and patients characteristics, possibly identifying predictive factors of efficacy. Most of the trials including only patients receiving carboplatin [8-13] were conducted in Asian subjects. However, several other trials [14-16] were conducted on a global scale and, in our opinion, the result can be reasonably applied to all patients independently of ethnicity.

In addition, one of the eligible trials [16] could not be included in the meta-analysis because data on the outcome selected (CR) were not available; nevertheless, the reported rate in terms of absence of vomiting confirmed the trend towards an advantage of the antiemetic triplet as compared to standard prophylaxis [16].

Finally, the endpoint CR defines a success as the absence of emesis and no need of rescue drugs, which does not explicitly include nausea. A patient with significant nausea, in the absence of rescue medications, would be defined as a success, although the impact of nausea on QoL could be relevant. Nausea is challenging, because of its subjective nature, and evaluation methods have not evolved in the last decades [22]. Among the studies included in our meta-analysis, nausea assessment was variable, with two trials using a visual analogue scale (VAS) [11,14], five trials evaluating nausea through questionnaires rating the most severe episode that occurred each day [8-10,12,14]. Moreover, assessment scales differ among studies, ranging from a two-point (“nausea” and “no nausea”) to a five-point scale. For two studies [15,16], no data on nausea were available. Bearing in mind these limitations, we described, as a secondary endpoint, the NK1RA efficacy on nausea control, showing a significant improvement with the addition of NK1RA, particularly in the delayed phase.. However, because nausea greatly affects patients’ QoL, future harmonization of reporting tools in trials evaluating drugs for CINV management should be a priority, in order to allow for a more accurate comparison and synthesis of the results [23]. Moreover, we believe that the development of a tool

assessing longitudinally symptoms such as nausea would add new insights in CINV management.

In conclusion, the results of our meta-analysis - along with the results of another systematic review published in 2017 [24] - underline the benefit of a triple anti-CINV premedication incorporating NK1RA for carboplatin-based regimens, as compared to 5-HT3RA plus dexamethasone prophylaxis. Considering all the available evidence, the entity of this benefit is comparable to the benefit obtained with the same combination in cisplatin- or antracyclines-based regimens, representing robust evidence to support recommendation in clinical practice guidelines.

Figure legends

Figure 1. PRISMA diagram of the study flow for the systematic review and meta-analysis.

Figure 2. Bar graph showing percentage of patients achieving complete response during the 120 hours following carboplatin-based chemotherapy administration. Complete response was defined as no vomiting and no use of rescue medication. Black bars regimen including NK1 receptor antagonist, 5HT3 receptor antagonist and dexamethasone, dotted bars regimen including 5HT3 receptor antagonist and dexamethasone. Acute phase = 0–24 hours post-chemotherapy, delayed phase = 25–120 hours post-chemotherapy; overall phase = 0–120 hours post-chemotherapy.

Figure 3. Forest plots *o*f odds ratios (OR) of complete response from randomized trials testing the addition of a NK1 receptor antagonist to 5HT3 receptor antagonist plus dexamethasone, in patients receiving carboplatin-based chemotherapy. Pooled ORs were computed using random-effect models. The bars indicate 95% confidence intervals (CI). Panel A: acute phase (0–24 hours post-chemotherapy); Panel B: delayed phase (25–120 hours post-chemotherapy); Panel C: overall phase (0–120 hours post-chemotherapy).

Figure 4. Forest plots *o*f odds ratios (OR) of no nausea from randomized trials testing the addition of a NK1 receptor antagonist to 5HT3 receptor antagonist plus dexamethasone, in patients receiving carboplatin-based chemotherapy. Pooled ORs were computed using random-effect models. The bars indicate 95% confidence intervals (CI). Panel A: acute phase (0–24 hours post-chemotherapy); Panel B: delayed phase (25–120 hours post-chemotherapy); Panel C: overall phase (0–120 hours post-chemotherapy).

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Conflicts of interest statement:

Massimo Di Maio had roles as advisor, and speaker's fee for Merck Sharp & Dohme, AstraZeneca, Bayer, Janssen, Bristol Myers Squibb, and Eli Lilly. Emilio Bria had roles as advisor, and speakers' fee for Merck Sharp & Dohme, AstraZeneca, Celgene, Pfizer, Eli-Lilly, Bristol Myers Squibb, and Novartis. All remaining authors declared no conflicts of interest.

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Table 1. Characteristics of the eligible trials

Study	Type of study	Label	Randomization procedure	Chemotherapy	Experimental arm	Control arm
Tanioka, 2013 [8]	Randomized phase II trial	Placebo	Computer-generated, blinded allocation schedule	Carboplatin (AUC5 or AUC6) plus paclitaxel or pemetrexed or liposomal doxorubicin*	Day 1: Aprepitant 125 mg; granisetron 1 mg IV; dexamethasone 12 mg IV. Day 2 and 3: Aprepitant 80 mg; Dexamethasone 4 mg IV.	Day 1: Granisetron 1 mg IV; dexamethasone 20 mg IV. Day 2 and 3: Dexamethasone 8 mg IV.
Ito, 2014 [9]	Randomized phase II trial	Open label	Central procedure, computer-generated	Carboplatin AUC 6 plus paclitaxel or pemetrexed (+/- bevacizumab)	Day 1: Aprepitant 125 mg; 1st generation 5-HT3 antagonist; dexamethasone 8 mg. Day 2 and 3: Aprepitant 80 mg; dexamethasone 8 mg.	Day 1: 1st generation 5-HT3 antagonist; dexamethasone 8 mg. Day 2 and 3: dexamethasone 8 mg.
Kusagaya, 2015 [10]	Randomized phase II trial, selection design	Open label	Central procedure, computer-generated	Carboplatin AUC6 plus paclitaxel or nab-paclitaxel or S-1 or pemetrexed (+/- bevacizumab)	Day 1: Aprepitant 125 mg; palonosetron 0.75 mg; dexamethasone 8 mg. Day 2 and 3: aprepitant 80 mg; dexamethasone 8 mg.	Day 1: palonosetron 0.75 mg; dexamethasone 8 mg. Day 2 and 3: dexamethasone 8 mg.
Kaushal, 2015 [11]	Randomized trial, no further details	Open label	No details	Carboplatin 300 mg/sm + docetaxel + 5-fluorouracil	Day 1: aprepitant 125 mg; palonosetron 0.25 mg IV; dexamethasone 12 mg IV. Day 2 and 3: Aprepitant 80 mg; Dexamethasone 8 mg orally BID.	Day 1: ondansetron 16 mg IV; dexamethasone 12 mg IV. Day 2 and 3: Ondansetron 8 mg orally BID; Dexamethasone 8 mg orally BID.

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Table 1. Characteristics of the eligible trials (continued)

Study	Type of study	Label	Randomization procedure	Chemotherapy	Experimental arm	Control arm
Maehara, 2015 [12]	Randomized trial, no further details	Open label	Sealed opaque envelopes	Carboplatin plus paclitaxel	Day 1: Aprepitant 125 mg; 5-HT3 antagonist 3 mg IV; dexamethasone 8 or 16 mg IV. Day 2 and 3: aprepitant 80 mg; dexamethasone 4 or 8 mg orally.	Day 1: 5-HT3 antagonist 3 mg IV; dexamethasone 8 or 16 mg IV. Day 2 and 3: dexamethasone 4 or 8 mg orally.
Yahata, 2016 [13]	Randomized, phase II-III trial	Placebo	Central procedure.	Carboplatin (AUC 5 or 6) plus paclitaxel	Day 1: aprepitant 125 mg; ondansetron 4 mg or granisetron 1 mg; dexamethasone 20 mg IV. Day 2 and 3: aprepitant 80 mg.	Day 1: ondansetron 4 mg or granisetron 1 mg; dexamethasone 20 mg IV. Day 2 and 3: no prophylaxis.
Hesketh, 2016 [14]	Subgroup analysis of a randomized phase III trial	Placebo	Web-based, central procedure.	Carboplatin alone or in combination with other cytotoxic drugs.	Day 1: rolapitant 180 mg; granisetron 2 mg orally; dexamethasone 20 mg orally. Day 2 and 3: granisetron 2 mg orally.	Day 1: granisetron 2 mg orally; dexamethasone 20 mg orally. Day 2 and 3: granisetron 2 mg orally.
Weinstein, 2016 [15]	Subgroup analysis of a randomized phase III trial	Placebo	Web-based, central procedure.	Carboplatin-based chemotherapy	Day 1: fosaprepitant 150 mg IV; ondansetron orally 8 mg + 8 mg after 8 hours; dexamethasone 12 mg orally. Day 2 and 3: no prophylaxis.	Day 1: ondansetron 8 mg orally + 8 mg after 8 hours; dexamethasone 20 mg orally. Day 2 and 3: ondansetron 8 mg orally BID.
Gralla, 2010 [16]	Subgroup analysis of a randomized phase III trial	Placebo	Computer-generated procedure.	Carboplatin-based chemotherapy	Day 1: aprepitant 125 mg; ondansetron orally 8 mg + 8 mg after 8 hours; dexamethasone 12 mg orally. Day 2 and 3: aprepitant 80 mg.	Day 1: ondansetron 8 mg orally + 8 mg after 8 hours; dexamethasone 20 mg orally. Day 2 and 3: ondansetron 8 mg orally BID.

**1 patient only did not receive carboplatin-based treatment and received 5-fluorouracil + leucovorin + irinotecan*

Table 2. Primary endpoint: complete response (no emesis, no use of rescue medication)

Study	Acute phase		Delayed phase		Overall period	
	Experimental	**Control**	**Experimental**	**Control**	**Experimental**	**Control**
Tanioka, 2013 [8]	44 / 45 (97.8%)	44 / 46 (95.7%)	28 / 45 (62.2%)	24 / 46 (52.2%)	28 / 45 (62.2%)	24 / 46 (52.2%)
Ito, 2014 [9]	65 / 66 (98.5%)	66 / 67 (98.5%)	54 / 66 (81.8%)	46 / 67 (68.7%)	53 / 66 (80.3%)	45 / 67 (67.2%)
Kusagaya, 2015 [10]	41 / 41 (100%)	39 / 39 (100%)	33 / 41 (80.5%)	30 / 39 (76.9%)	33 / 41 (80.5%)	30 / 39 (76.9%)
Kaushal, 2015 [11]	26 / 30 (86.7%)	18 / 30 (60.0%)	25 / 30 (83.3%)	16 / 30 (53.3%)	25 / 30 (83.3%)	16 / 30 (53.3%)
Maehara, 2015 [12]	11 / 11 (100%)	6 / 12 (50.0%)	11 / 11 (100%)	8 / 12 (66.7%)	11 / 11 (100%)	5 / 12 (41.7%)
Yahata, 2016 [13]	142 / 151 (94.0%)	132 / 146 (90.4%)	96 / 151 (63.6%)	72 / 146 (49.3%)	93 / 151 (61.6%)	69 / 146 (47.3%)
Hesketh, 2016 [14]	176 / 192 (91.7%)	184 / 209 (88.0%)	158 / 192 (82.3%)	137 / 209 (65.6%)	154 / 192 (80.2%)	135 / 209 (64.6%)
Weinstein, 2016 [15]	243 / 257 (94.6%)	236 / 256 (92.2%)	201 / 257 (78.2%)	164 / 256 (64.1%)	200 / 257 (77.8%)	162 / 256 (63.3%)
Gralla, 2010 [16]	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
OVERALL	**748 / 793 (94.5%)**	**725 / 805 (90.1%)**	**606 / 793 (76.4%)**	**497 / 805 (61.7%)**	**597 / 793 (75.3%)**	**486 / 805 (60.4%)**