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Efficacy and safety of antiemetic regimens for highly emetogenic chemotherapy-induced nausea and vomiting: A systematic review and network meta-analysis

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ABSTRACT

Background: Several regimens have been introduced in clinical practice in the last twenty years to treat chemotherapy-induced nausea and vomiting (CINV). However, direct comparative data remain insufficient, as many new regimes lack head-to-head comparisons. In this study, through an indirect comparison, we overcome this limit by providing the most up-to-date estimate of the efficacy and safety of all combinations used for HEC-induced nausea and vomiting.

Patients and methods: We retrieved randomized controlled trials (RCTs) published in Pubmed, Embase, and Cochrane Library until June, 30th 2022. We included phase II-III RCTs, including adults with any cancer receiving HEC, and compared different antiemetic regimes to prevent CINV. The primary outcome was the overall complete response (defined as the absence of vomiting and of the use of rescue drugs from 0 to 120 hrs since chemotherapy); secondary outcomes were acute (absence of vomiting and use of rescue medicine 0–24 hrs after chemotherapy) and delayed (24–120 hrs) response and adverse events.

Results: A total of 53 RCTs enrolling 22 228 patients were included. We classified the different antiemetic regimes into 21 different groups. Overall, 3- or 4-drug regimens containing a combination of dexamethasone, 5HT3 antagonists, mirtazapine or olanzapine with or without NK antagonists, yielded the highest probability to be the most effective regimen in terms of complete response. Regimens containing a combination of dexamethasone and 5-HT3 antagonist have the lowest probability of being the most effective regimen in terms of complete, acute, and delayed response.

Conclusion: In our network meta-analysis, 4-drug regimens with olanzapine displayed the highest probability of efficacy in terms of complete response. A 3-drug regimen with olanzapine represents a valid option in a limited resource context.

Introduction

Chemotherapy-induced nausea and vomiting (CINV) are common and distressing side effects. 70 % to 80 % of cancer patients receiving chemotherapy develop CINV; without appropriate therapy, the risk of developing CINV rises to 90 % of patients with highly-emetogenic-chemotherapy (HEC) [1–3]. CINV is linked with worse quality of Life, treatment compliance, malnutrition, and, cognitive disorders, with a potential impact on anti-cancer treatment efficacy [4–6]. The treatment goal for CINV should be to avoid the first occurrence of CINV. Once

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patients experience CINV, they are four times more likely to experience nausea and vomiting in subsequent cycles of chemotherapy [7]. To date, clinically effective agents are available to prevent or treat CINV, including 5-hydroxytryptamine type 3 receptor antagonists (5-HT3 RA), neurokinin 1 receptor antagonists (NK1 RA), dexamethasone, and antipsychotic agents. In addition, other drug classes, such as cannabinoids, and benzodiazepines, can be used in CINV treatment [8,9].

NCCN/ASCO guidelines are convergent on 3-drugs (NK1 RA, 5HT3 RA, and dexamethasone (DEX) regimen +/- olanzapine (OLA) for managing HEC. All these regimens have a strong recommendation, lacking a clear indication of which should be preferably prescribed due to the scarce head-to-head comparisons. In contrast, MASCC/ESMO guideline recommended as the landmark for CINV prevention by HEC a 3-drug regimen with NK1 RA, 5HT3 RA, and DEX. Adding OLA is an option with a lower grade of evidence and recommendation.

Our study aims to offer an updated, comprehensive systematic review of all randomized controlled trials (RCTs) investigating antiemetic combinations for patients treated with HEC to generate a clinically meaningful treatment ranking according to efficacy and safety.

Materials and methods

Search strategy

We performed this systematic review and network meta-analysis according to the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) extension statement for network meta-analysis. We used a completed PRISMA 2020 checklist to illustrate the methodology of our study (Appendix 1). The protocol for this review was previously published in the PROSPERO database (n° CRD42021272799).

We included phase II-III RCTs, requiring full journal publication and excluding unpublished clinical trials and abstracts even if they had sufficient data for analysis. We included blinded and non-blinded studies and addressed the potential impact of blinding in our bias assessment and sensitivity analyses. Considering that most of trials have as their primary endpoint the assessment of response to the first cycle of chemotherapy, only results from the first cycle were included, excluding cross-over studies if the results according to treatments were unclear. We excluded studies that were cluster-randomized or non-randomized, as well as case reports and clinical observations.

Inclusion criteria

Types of participants and interventions

Studies included trials involving adult patients according to the definition provided in the studies (≥18 years of age), with a histopathologically confirmed cancer diagnosis, irrespective of type and stage of cancer and gender. We included both patients with solid cancer and patients with haematological malignancies. While there are several guidelines defining the emetogenicity of chemotherapy, we included studies based on the latest definition of HEC provided by the Multinational Association of Supportive Care in Cancer (MASCC)/European Society of Medical Oncology (ESMO) [10] in 2016, regardless of whether the study authors classified the emetogenic chemotherapy as high risk. We classified 5-HT3 RA in 1st (ondansetron, granisetron, and ramosetron) and 2nd generation (palonosetron). Similarly, NK-1 RA were divided in 1st (aprepitant, fosaprepitant) and 2nd (netupitant, fosnetupitant) generation. We considered olanzapine separately, based on the two different dosages (5 mg OLA 5 and 10 mg OLA 10). We compared combinations of these interventions at any dose and by route versus each other in a full network. We included all RCTs comparing the intervention of interest in at least one arm. In particular, different drugs of the same class were grouped according to the generation in the comparisons. Different doses of the same agent were considered separately. An overview of all included experimental treatment regimens is provided in Supplementary Table 1. We excluded trials including patients receiving both HEC and moderate emetogenic chemotherapy (MEC), which did not provide subgroup data for each emetogenic risk group, and trials evaluating participants at risk for radiotherapy-induced nausea and vomiting. At the time this network meta-analysis (NMA) was compiled, MASCC/ESMO guidelines recommended antiemetics for prophylaxis of CINV caused by HEC included either 5-HT3 RA, corticosteroids and NK-1 RA combinations [10].

We excluded trials in which the antiemetics were not administered before chemotherapy. Included trials should have been comparable in terms of clinical and methodological criteria to hold for transitivity. Therefore, we excluded trials published before 1999 evaluating a one-drug arm as a control arm. We excluded these trials, as they considered drugs that are no longer recommended for primary prophylaxis of CINV in HEC, and these trials might be outdated. As per current MASCC/ESMO guidelines for CINV prevention, regimens containing DEX + 1st 5HT3 RA + 1st NK-1 RA were used as the control arm in this NMA, while other drug combinations were considered experimental.

Types of outcome measures and objectives

We included all trials fitting the inclusion criteria mentioned above, irrespective of reported outcomes. In adults with solid cancer or haematological malignancy receiving HEC, we estimated the relative ranking of competing interventions:

- To compare the effects of antiemetic treatment combinations, including NK-1 RA, 5-HT3 RA, and DEX, on prevention of acute phase (0–24 h since chemotherapy), delayed phase (24–120 h since chemotherapy), and overall (0–120 h since chemotherapy) CINV in network meta-analysis
- To generate a clinically meaningful treatment ranking according to treatment safety and efficacy

The primary outcome measure is complete response (CR) (absence of vomiting and use of rescue medicine) measured within the 0–120-hours frame. Secondary outcomes include CR within 0–24 h, CR within 24–120 h, and safety (adverse events G3-G4).

Search methods for identification of studies

We searched PubMed, Cochrane, and Web of Science databases. In addition, we explored the conference proceedings of annual meetings of the principal societies (ASCO, ESMO, and MASCC). The search was conducted on June, 30th 2022. We searched for all possible comparisons formed by interventions of interest. We used medical subject headings (MeSH) or equivalent and text word terms and did not apply language restrictions and tailored searches to individual databases. The search strategies used can be found in Supplementary Tables 2A and B.

Two review authors (M.F. and P.L.) independently screened the results of the search strategies for eligibility for this review by reading the abstracts using Rayyan.

In the case of disagreement, or if it was unclear whether we should have retrieved the abstract, we obtained the full-text publication for further discussion. Independent review authors excluded records that did not meet the inclusion criteria and obtained full-text copies of the remaining records. Two review authors (M.F. and P.L.) assessed these records independently against our pre-defined eligibility criteria to identify relevant studies. In the event of disagreement, we adjudicated a third review author (R.G.).

Data extraction

Two investigators independently extracted the following information from the included articles: General information (author, title, source, publication date, country, language, duplicate publications),

elements of risk of bias assessment (sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, other sources of bias), study characteristics (trial design, aims, setting and dates, source of participants, inclusion/exclusion criteria, comparability of groups, subgroup analysis, statistical methods, power calculations, treatment cross-overs, compliance with assigned treatment, length of follow-up, time point of randomisation), participant characteristics (age, gender, ethnicity, number of participants recruited/allocated/evaluated, cancer type and stage, additional diagnoses, type and intensity of antineoplastic therapy, other patient-specific prognostic factors like as pregnancy and alcohol intake), interventions and comparators (type and dosage of antiemetic agents, duration of prophylaxis, duration of follow-up), outcomes (complete response in overall, acute and deleyed phase, adverse events, and serious adverse events). A consensus of all the investigators resolved all the discrepancies regarding data extraction.

Risk of bias assessment

Two authors (P.L. and M.F.) independently assessed the potential

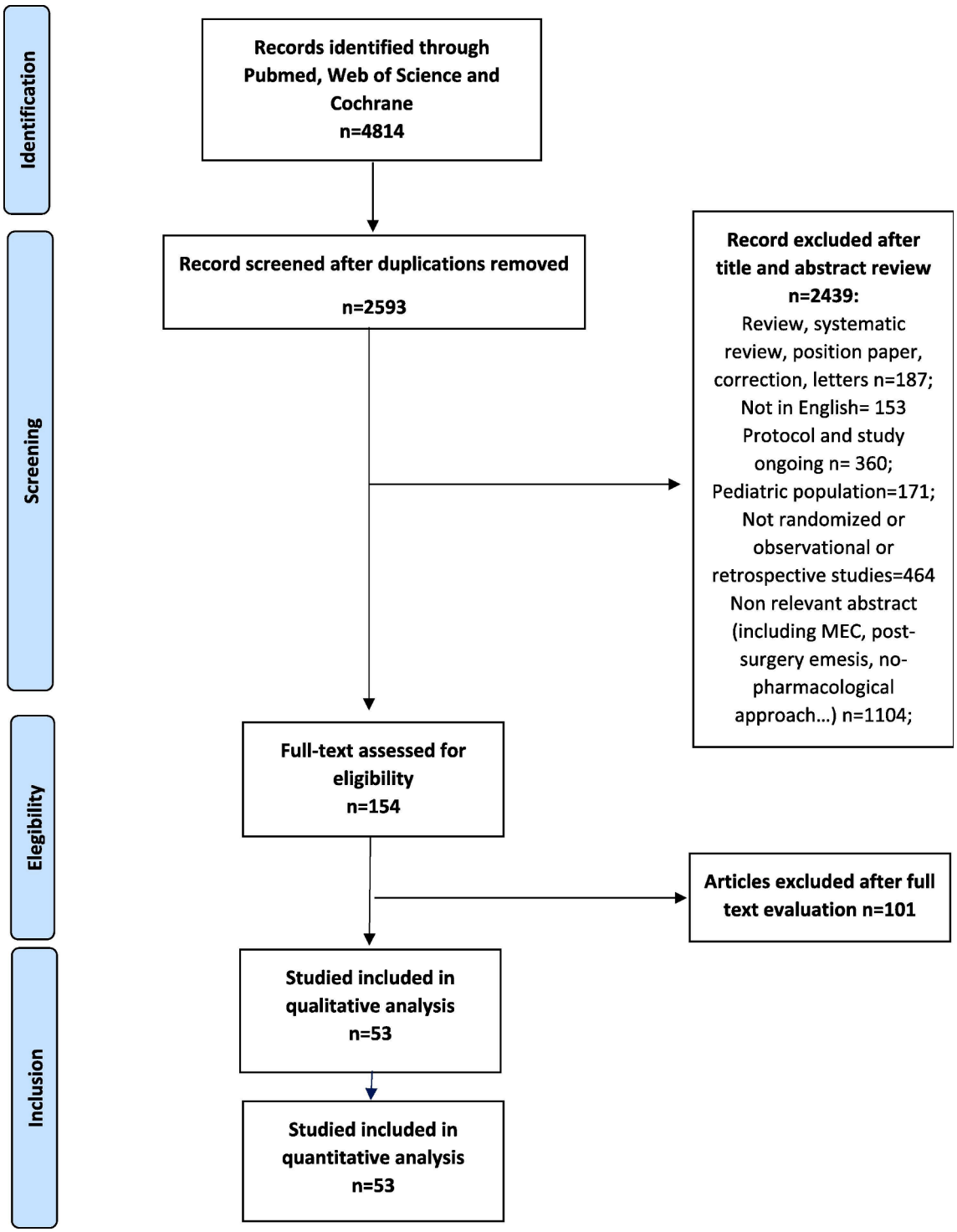

Fig. 1. Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) diagram;

risk of bias in the selected studies by using the "Cochrane Collaboration tool for assessing the risk of bias in randomized trials" [11] (Supplementary Figures 1 and 2). A consensus among all the authors resolved potential disagreements.

Statistical analyses

An NMA was applied to randomized clinical trials to evaluate the effects of multiple treatment comparisons in a frequentist approach. Direct and indirect effects were estimated to give clinical evidence. Preliminary heterogeneity was evaluated by using the chi-square ($\chi 2$), I-square (I2), and Q tests, with the significance set at I2 > 50 % or P < 0.05. When the heterogeneity tests were significant, a random-effect analysis model was applied. Otherwise, a fixed-effect model was used. An independent network meta-analysis was performed for each outcome measure: treatment effects were estimated by ORs and their corresponding 95 % CI. Also, network plots were drawn because the network graph visualization supported undirected and directed graph structures. This type of visualization highlighted relationships between treatments. In addition, the frequentist P-scores achieved a treatment ranking, considered a frequentist version of the SUCRA. The P-scores measure the extent of certainty that a treatment is better than another averaged over all competing treatments. The network meta-analyses were performed using R software (version 4.2.1) (R Core Team, 2021) and netmeta package [12].

Results

Characteristics of included trials

We identified 4814 potentially relevant references through literature research. After removing the duplications, 2593 papers remained to be analysed. Screening the title and abstract, we selected 154 articles for extensive analysis. After the full-text screening, 53 papers fulfilled the inclusion criteria and were included in our systematic review. We summarized the main features of the included studies in Supplementary Table 3. We documented the total number of screened, selected, and excluded studies in a prism flow diagram (Fig. 1).

We included 53 studies enrolling 22.228 patients. The studies were published between January 1999 and June 2022. The sample size ranged from 40 patients to 1455. Thirty-one studies (61 %) enrolled exclusively Asian patients, the remaining 20 studies mostly Caucasian patients, while the African American patients enrolled were a minority, being included in only seven studies (in a variable range between 0.2 % and 5.5 % of enrolled patients). Finally, two studies did not provide details on the race of the patients enrolled. Seven studies enrolled only breast cancer patients treated with a combination of cyclophosphamide and anthracyclines. In contrast, 27 studies (53 %) used cisplatin-based chemotherapies at a dosage $\geq$ 50 mg/m^2. In most studies (36/53, 68 %), patients were naive to chemotherapy treatments at the inclusion. According to the different regimens, we sorted 21 treatment groups. Thirty-eight studies investigated a three-drug combination of an NK-1 RA, a 5-HT3 RA, and DEX; seven studies used a three-drug combination with OLA instead of NK-1 RA, while seven studies involved the use of a 4-drugs combination of NK-1 RA, 5-HT3 RA, DEX with the addition of either OLA (6 trials) or mirtazapine (NaSSA) (1 trial). Finally, one study used 5-HT3 RA, DEX, and thalidomide as the experimental arm.

Aprepitant was the most used NK-1 RA (32/53 studies, 60 %), followed by the fosaprepitant (N = 6), netupitant (N = 4) and the fosnetupitant (N = 3). The second-generation palonosetron was used in 25 studies, while the first-generation antagonists were in 28.

Overall response (0 to 120 h)

Overall Compete response (0–120 h) was reported in 52 studies, including 21,877 participants, while one study did not have the overall CR among the endpoints analyzed. These studies were analyzed using conventional and network meta-analysis approaches (Supplementary Table 4). The network plot of this outcome is depicted in Fig. 2A. Fig. 2B reports odds ratio (OR) and confidence intervals (CIs) of all treatments. Five regimens demonstrated a significantly increased activity compared to the standard regimen: four encompassed 4-drug regimens (one with NaSSA and 3 with OLA), irrespective of the generation of 5HT3 RA, while the latter was a one NK-1 RA-free regimen OLA-based. We observed moderate heterogeneity (I2 = 59.5 %) between studies in this network.

Table 1 presents the ranking of treatments based on cumulative probability plots and surfaces under the cumulative ranking (SUCRAs). The regimen DEX + 2nd 5-HT3 RA + 1st NK-1 RA + NaSSA (p-score 0.89) had the chance for the highest response in the overall phase, followed by DEX + 2nd 5-HT3 RA + 1st NK-1 RA + OLA 5 (p -score 0.88), DEX + 1st 5-HT3 RA + 1st NK-1 RA + OLA 10 (p-score 0.88), DEX + 2nd 5-HT3 RA + 1st NK-1 RA + OLA 10 (0.81), DEX + 2nd 5-HT3 RA + 2nd NK-1 RA (p-score 0.78). On the contrary, regimens containing a combination of DEX and 5-HT3 RA confirm that they have the lowest probability of being the best treatment in the overall phase.

Acute response (0 to 24 h)

Forty-seven studies reported CR data in the acute phase, including 16,659 patients treated with 21 experimental antiemetic combinations. Supplementary Figure 3A reported the results of the NMA for the CR in the acute phase. We observed moderate heterogeneity (I2 = 66.5 %) between studies in this network.

In Supplementary Figure 3B, we reported OR and 95 % CIs of all treatments. DEX + 2nd 5HT3 RA and OLA 10, DEX + 2nd 5HT3 RA + 1st NK-1 RA, and OLA 10 showed significantly higher CR in the acute phase than the standard regimen. No other combination showed significant differences in CR in the acute phase. Supplementary Table 5 shows the ranking profiles of the p-score for all the analyzed combinations. A combination of DEX + 1st 5-HT3 RA + 1st NK-1 RA + OLA 5 had the highest probability of CR in the acute phase (p-score 0.86), followed by two other OLA-based regimens, DEX + 2nd 5- HT3 RA + 1st NK-1 RA + OLA 10 (p-score 0.85) and DEX + 2nd 5-HT3 RA + OLA 10 (p-score 0.84). By contrast, the two-drug regimens DEX + 2nd 5-HT3 RA and DEX + 1st 5-HT3 RA had the lowest probability of being the most effective treatment (p-score 0.13 and 0.08, respectively).

Delayed response (24 to 120 h)

We analyzed CR data during the delayed phase of 49 studies, enrolling 19,923 patients. In Supplementary Figure 4A, we report the results of the NMA for the CR in the delayed phase. The analyzed studies showed moderate heterogeneity (I2 57 %). Supplementary Figure 4B reports the OR and ICs of all the analyzed combinations. Overall, five regimes showed a statistically significant advantage over the standard treatment. In particular, four regimens consisted of a 4-drugs combination of NK-1 RA, 5-HT3 RA, DEX, and OLA (n = 3) or NaSSA (n = 1). The last regimen was an NK-1 RA-free combination of DEX, 2° 5HT3 RA, and OLA. The combination DEX + 1st 5-HT3 RA + 1st NK-1 RA + OLA 10 yielded the best probability to be the most effective treatment in the delayed phase (p-score 0.95), followed by DEX + 2nd 5-HT3 RA + 1st NK-1 RA + NaSSA (p-score 0.88), DEX + 2nd 5-HT3 RA + 1st NK-1 RA + OLA 5 (p-score 0.85) and DEX + 2nd 5-HT3 RA + OLA 10 (p-score 0.77) (Supplementary Table 6).

Safety

Participants with at least one G3-4 AE were reported in 23 studies for ten treatments. Results for all network comparisons, including the ranking of treatments, are shown in Supplementary Figures 5A- 5B and Supplementary Table 7). We observed low heterogeneity (I2 = 7.6 %)

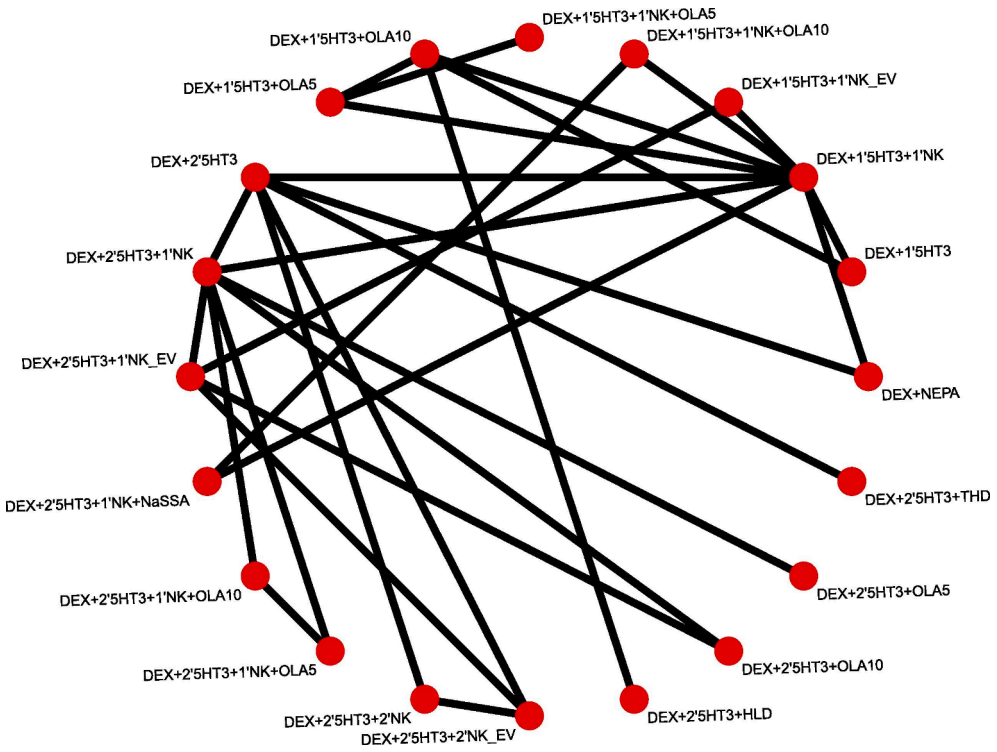

Fig. 2a. Network graph for the outcome complete response of CINV in the overall phase;

between studies in the network. Overall, none of the investigated regimens differed in a statistically significant manner from the reference treatment. The 2-drug regimen with DEX + 5-HT3 yielded the best probability of being the safest treatment, while the 4-drug regimens have the highest probability of grade 3–4 toxicity.

Discussion

We performed this NMA intending to define, through direct and indirect comparison, which regimen, among those available, warrants the best activity in preventing CINV in patients receiving HEC. We found that using all the available drugs, including olanzapine/mirtazapine, yields the highest probability of exerting the maximum activity. On the other hand, patients experienced low levels of serious (G3-4) AEs, with a two-drug combination yielding the highest probability of showing the most tolerable profile.

To our knowledge, this is the first meta-analysis for preventing CINV from HEC that includes OLA-based regimens.

A similar systematic review and NMA was conducted by Piechotta et al. in 2021 [13]. They included regimens for preventing CINV in patients receiving either HEC or MEC, excluding those combinations that comprised OLA. Limited to the HEC-receiving patients, they concluded, with moderate certainty, that fosaprepitant + palonosetron (and DEX) was most probably the best regimen for preventing HEC-determined CINV. With this NMA, we add that combining OLA yields an even better score being the best treatment with similar or slightly higher certainty.

In 2016, the ESMO-MASCC task force recommended a combination of DEX- 5HT3 and NK1 RA as the mainstay of treatment, potentially adding olanzapine, though this was based on a modest level of evidence. In contrast, ASCO guidelines strongly recommended quadruplets (including OLA) for the prophylaxis of CINV by HEC with high-quality evidence [3].

Our data could be a starting point to improve the ESMO-MASCC task force recommendations [10] with the latest evidence that quadruplets reasonably represent the treatment of choice in preventing CINV from HEC based on trials prone to low risk of bias demonstrating meaningful activity. Moreover, the central role of these drugs is reinforced, in our model, by the fact that NK1 RA free triplet (with 10 mg OLA) scored very close to the quadruplets in terms of overall antiemetic response and was slightly better than NK1-based triplets (our reference) or even NEPA combination.

Based on these considerations, it is quite unexpected that OLA is neither convincingly perceived as part of the standard treatment nor clinical trials. Recent data, indeed, showed how a low proportion of patients receive OLA-based triplets[14] in clinical practice. Moreover, OLA is included as part of the investigated treatments in only 7 out of 43 trials conducted since the first positive randomized clinical trial study involving the addition of OLA published in 2011[15].

Our results are relevant because they incorporate the most updated evidence in this rapidly changing field. The question of the most effective regimen for CINV prevention is a clinically significant problem due to the incidence of this event and the costs associated with its management. A retrospective study showed that despite prophylactic treatment, 47,988 CINV events occurred in the follow-up period with an associated all-cause treatment cost of US $89 million[16]. Optimal use of the CINV regimen could help prevent these costs. Moreover, OLA implementation, though equally effective or slightly better, permits savings compared to NK1 RA triplets, being a viable option in low/middle-income countries or wherever NK1 RA is unavailable.

Moreover, optimization of CINV (including NaSSA) represents, in our view, the research basis for reducing doses of DEX in CINV prevention regimen, potentially favoring positive outcomes in cancer patients. For example, reducing DEX for CINV prevention could be crucial to prevent the long-term side effects of steroid therapies, such as weight gain, the onset of diabetes or metabolic syndrome, or osteoporosis[17] in those patients whose survival is increasing due to more effective anticancer treatments.

We acknowledge that our work bears some limits. First, it does not substitute adequately powered head-to-head trials. The indirect comparison does not have enough power in comparing any treatment with each other.

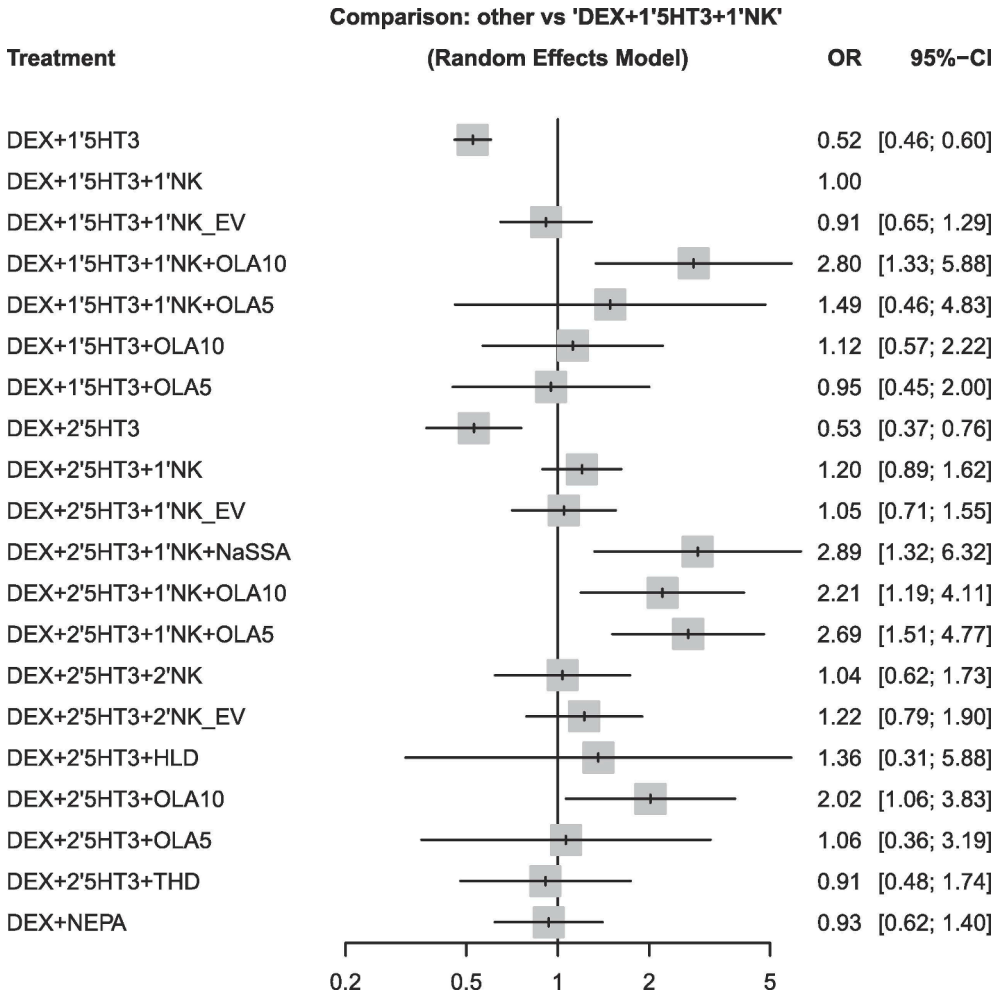

Fig. 2b. Network meta-analysis forest plot for the outcome complete response of CINV during the overall phase;

Table 1
Analysis of the treatment ranking according to the outcome complete response of CINV during the overall phase.

Combinazione	P-score
DEX + 2° 5-HT3 + 1° NK + NaSSA	0.8916
DEX + 2° 5-HT3 + 1° NK + OLA 5	0.8892
DEX + 1° 5-HT3 + 1° NK + OLA 10	0.8850
DEX + 2° 5-HT3 + 1° NK + OLA 10	0.8182
DEX + 2° 5-HT3 + OLA 10	0.7850
DEX + 1° 5-HT3 + 1° NK + OLA 5	0.6067
DEX + 2° 5-HT3 + 2° NK EV	0.5493
DEX + 1° 5-HT3 + HLD	0.5442
DEX + 2° 5-HT3 + 1° NK	0.5344
DEX + 1° 5-HT3 + OLA 10	0.4635
DEX + 2° 5-HT3 + OLA 5	0.4320
DEX + 2° 5-HT3 + 1° NK EV	0.4132
DEX + 2° 5-HT3 + 2° NK	0.4081
DEX + 1° 5-HT3 + 1° NK	0.3734
DEX + 1° 5-HT3 + OLA 5	0.3520
DEX + 2° 5-HT3 + THD	0.3264
DEX + NEPA	0.3263
DEX + 1° 5-HT3 + 1° NK EV	0.3064
DEX + 2° 5-HT3	0.0493
DEX + 1° 5-HT3	0.0460

Second, we chose CR (that is absence of vomiting and absence of rescue medication for nausea and vomiting) instead of complete control (including the absence of nausea). Therefore, we could have labeled a patient without vomiting and rescue medication within the timeframe considered as a responder even if he/she experiences a substantial (not requiring medications) nausea. We are aware that this could overestimate the efficacy of the drugs. However, this endpoint was the most consistently reported in the trials we included and, perhaps most importantly, overestimation laid over all the regimens considered and did not favor anyone in particular. Finally, notwithstanding the heterogeneity of the trials we considered here, we did not pursue specified analyses based on those factors that could potentially affect the emetogenic potential of diverse chemotherapy regimens as well as response to antiemetics (alcohol intake and BMI). Unfortunately, very few trials specifically included these characteristics in the report, although we tried to standardize some of these (chemotherapy regimens defined as HEC) through the most updated and accepted definitions (MASCC/ESMO 2016) instead of the Investigator attribution through the years.

In conclusion, we can suggest with moderate-good certainty 4-drugs regimens including OLA as the treatment of choice for preventing CINV in patients receiving HEC.

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Authors' contributions

All authors contributed to the publication according to the ICMJE guidelines for the authorship. All authors read and approved the

submitted version of the manuscript (and any substantially modified version that involves the author's contribution to the study). Each author has agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: R. G. declared financial interests with Roche (Expert Testimony, Personal, Advisory Board for Clinician's expertise on Drug Management), Molteni (Writing Engagement, Personal, Pubblication fee for open access manuscript), Novartis (Advisory Board, Personal, Advisory Board), Angelini Pharma (Invited Speaker, Personal, Invited Speaker to national and international congress), Pfizer (Advisory Board, Personal, Advisory Board) and Takeda (Expert Testimony, Personal, Expert testimony on Drug Managemen). F. S. reported personal/consulting fees from Pfizer, Bristol Myers Squibb, MSD, Roche, Pierre Fabre Oncology, Leo Pharma, Bayer, Mylan/Viatris, Mundi Pharma, Astellas, Vifor Pharma, Amgen, Arrow, Biogaran, and Helsinn and nonfinancial support from Pierre Fabre Oncology. G. S. has served as consultant for TESARO Bio Italy S.r.l and Johnson & Johnson. He received onoraria from Clovis Oncology Italy S.r.l, and institutional research funding from MSD Italy S.r.l. G. D. has served on advisory board of Beigene and received support for travel and accomodation from Roche. The other authors declare that they have no conflict of interest..

Data Availability Statement

Study data made available upon reasonable request.

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None.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctrv.2023.102512.

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