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Anti-emetic Recommendations for Breast Cancer Patients Receiving Highly-Emetogenic Chemotherapy: A Systematic Review incorporating Network Meta-analyses.

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BACKGROUND

- Anthracycline and Cyclophosphamide (A&C)-based chemotherapy (CT) regimens are considered highly emetic.
- Consensus guidelines (ASCO, MASCC / ESMO, NCCN, CCO) recommend patients receive combination of 5HT3 antagonist (day 1), NK1 receptor antagonist (days 1-3), and dexamethasone (day 1 only or days 1-3 +/- day 4).
- Despite widespread use of different anti-emetic regimens most patients will experience suboptimal emetic control.

OBJECTIVE

- To determine the optimal anti-emetic regimen to treat chemotherapy induced nausea and vomiting (CINV) in breast cancer patients receiving A&C-based chemotherapy using network meta-analysis
- To assess the evidence base of consensus anti-emetic guidelines
- To determine what future trials need to be performed

DATA SOURCES & DISCLAIMERS

- A peer reviewed literature search of Medline (1947-Nov 2013), Embase (1980-Nov 2013) and the Cochrane Collaboration's CENTRAL (Fall 2012 Issue) was performed.
- This study was not funded by the pharmaceutical industry

STUDY SELECTION

- **Patients:** Randomized, controlled trials (RCTs) assessing CINV in breast cancer patients (≥50% in RCT) on A&C chemotherapy (≥33% in RCT)
- **Intervention / Comparator:** CINV prophylaxis regimens
- **Primary Outcome (from 0-120 hours post-chemo):**

✓Total Control (No nausea + No vomiting + no rescue anti-emetics)

- **Secondary Outcomes (from 0-120 hours post-chemo):**

✓Complete Protection (Minimal nausea + No vomiting + No rescue)

✓No Nausea

✓Complete Response (No Vomiting + No rescue)

✓Acute and Delayed phases of above outcoms

FIGURE 1. Literature selection process for systematic review and network meta-analysis.

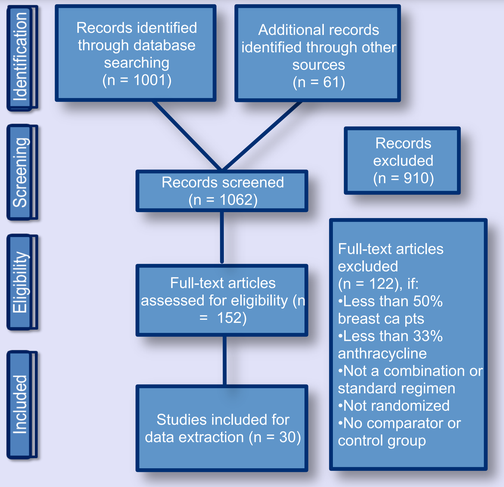


Table 1. Summary of Estimated Probabilities that each Treatment is Best

Anti-Emetic Regimen	P(best), RE model	P(best), FE model
5HT3 day 1, NK1>=day 1, STER>=day 1	2.45%	1.59%
5HT3 day 1, STER day 1	0.31%	0%
5HT3>=day 1, NK1 day 1, STER day 1	10.78%	2.74%
5HT3>=day 1, NK1>=day 1, STER day 1	6.9%	0.41%
5HT3>=day 1, STER day 1	0.79%	0%
5HT3 day 1, NK1>=day 1, STER day 1	4.04%	4.73%
5HT3 day 1, STER day 1, PRO>day 1	0.22%	0%
5HT3 day 1, STER>=day 1	0.01%	0%
5HT3 day 1, STER>=day 1, PRO>day 1	5.04%	1.74%
5HT3 day 1, NK1 day 1, STER>=day 1	2.87%	1.64%
5HT3 day 1, STER>=day 1, GABA>=day 1	40.28%	64.4%
5HT3>=day 1	0.03%	0%
5HT3 day 1, STER day 1, OLAN>=day 1	23.34%	21.66%
5HT3>=day 1, STER>=day 1	0.87%	0.5%
Other	2.07%	0.58%

FIGURE 2. Largest Network: 15 Treatments from 24 RCTs

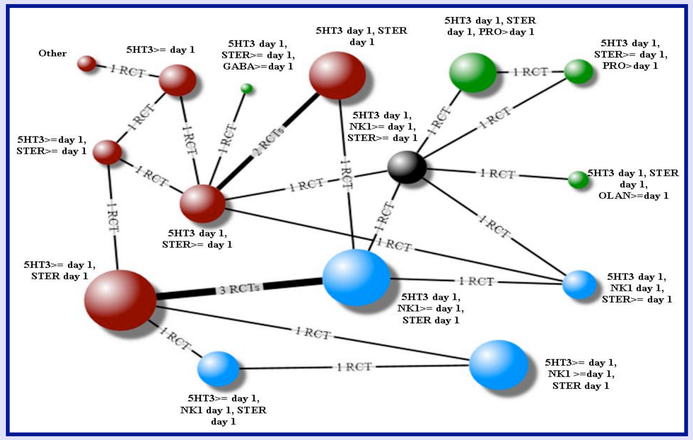
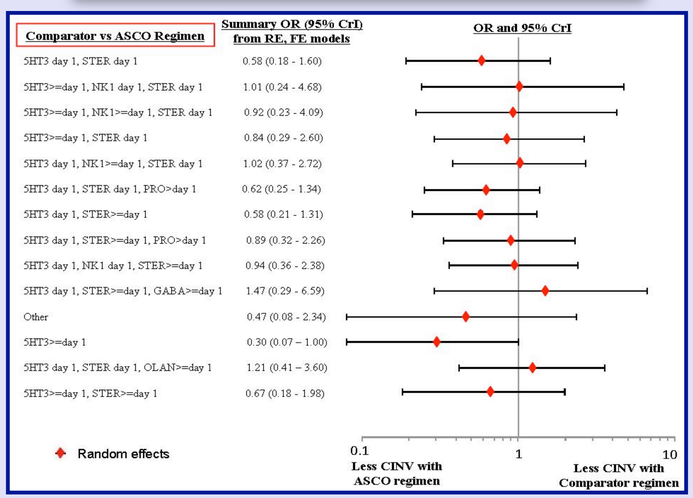


FIGURE 3. Odds Ratios (OR) of comparator antiemetic regimens vs. ASCO recommended regimen



NETWORK META-ANALYSIS

- 'Network meta-analysis' (NMA) enables us to link data from multiple trials comparing different treatment regimens into a single network to make indirect comparisons of treatments possible even where head-to-head trial data does not exist.
- NMA does not discover a new anti-emetic treatment, but helps to confirm or refute the validity of current recommendations
- A Bayesian network meta-analysis was performed to assess the relative effectiveness of different antiemetic regimens on Total control of CINV.
- We grouped treatments according to dosage and duration of steroids, 5HT3 antagonists, NK1 antagonists, and other added therapies in our network (Table 1).
- We present summary meta-analytic estimates with 95% credible intervals (Fig. 3). We also show the corresponding probabilities of each treatment being the best regimen (Table 1).

DISCUSSION

- Trials were heterogeneous in terms of study design, study population, chemotherapy regimens, anti-emetic regimens, and selection and reporting of patient risk factors and outcome measures
- We could not fully incorporate all regimens into a single network as a result
- Challenges with connectivity and discrepancies in treatment response rates have made it difficult to achieve a good model fit for the NMA
- Random effects model accounted for these exceptions, but most of the pair wise comparisons had wide credible intervals, and were inconclusive.
- Comparisons achieving statistical significance were based on indirect comparisons that have not been compared in a head-to-head trials
- Study heterogeneity makes direct comparisons challenging for physicians, patients, and guideline groups

CONCLUSION

- Total control of CINV remains uncommon
- While respecting consensus guidelines, our findings would suggest they are not supported well by all the available evidence
- Future studies should use standardized design and comprehensive reporting of outcomes.