Systematic review and individual patient data based meta-analysis of Palonosetron trials for chemotherapy-induced nausea and vomiting

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ABSTRACT

Introduction
Several clinical trials have evaluated the need for corticosteroid-containing antiemetic regimens on the days after the first 24 hours to control delayed chemotherapy-induced nausea and vomiting (CINV) during moderate emetogenic chemotherapy (MEC) or anthracycline and/or cyclophosphamide (AC)-containing chemotherapy.
Objectives
To evaluate whether the dexamethasone-sparing regimen is associated with a significant loss in overall antiemetic control using individual patient data (IPD) meta-analysis.
Methods
We conducted systematic review for any randomized trials reporting CINV outcomes for a single 1-day-dexamethasone (D1 group) containing antiemetic regimen in chemotherapy-naive adult patients scheduled to receive a MEC or AC-containing chemotherapy, compared with additional dexamethasone on days 2 and 3 (D3 group). The primary endpoint was complete response (CR) in the 5-day study period. Secondary endpoints were CR rates in 0–24 h and CR rates in 24–120 h; complete control in each period.
Results
All 5 eligible studies (N=1194) were enrolled in the meta-analysis. Overall, D1 group was not significantly inferior to D3 group in CR rate as well as complete control rate [pooled risk difference in CR rate -1.5%, 95% confidence interval -7.1–4.0%; in delayed CR rate -2.4%, 95% confidence interval -7.7–2.9%]. There was no significant interaction between dexamethasone regimen and patient characteristics (sex, age category (<60 or 60 years), and alcohol consumption).
Conclusions
These results strongly suggest that the dexamethasone-sparing regimen is not associated with a significant loss in overall antiemetic control in an adult patient undergoing MEC or AC-containing chemotherapy, irrespective of patient baseline characteristics.

METHODS

Background

- CINV severely influences patients' quality of life, and compliance with chemotherapy (Aapro 2007).
- Dexamethasone (DEX) is frequently used for the control of CINV and is administered on day 1-3 with palonosetron or NK1 receptor antagonist though DEX has several adverse effects(insomnia [45%] , GI symptoms [27%], etc). Continued use of DEX is also known to reduce bone mineral density.
- The current recommendations for the prevention of AC/MEC from NCCN, ASCO and MASCC for AC and MEC containing chemotherapy are controversial (NCCN 2015, ASCO2016, MASCC 2016).
- Several randomized controlled trials were conducted to evaluate whether the dexamethasone-sparing regimen is associated with a significant loss in overall antiemetic control in several countries.
- Systematic review and IPD based meta-analysis was planned in this study group.

Methods

- Following trial design were eligible and searched for the IPD meta-analysis (**Figure 1**). Pubmed/MEDLINE were searched by KO and YO.

Eligibility criteria
- Chemotherapy-naïve adult patient
- Enrolled after 2000
- No perioperative chemotherapy and other therapies (radiotherapy, immuno-therapy, and so on)

D-1 group	Day1	Day2	Day3	Day 4	Day5
PALO	●				
DEX	●				

D-3 group	Day1	Day2	Day3	Day 4	Day5
PALO	●				
DEX	●	●	●		

- The Primary endpoint: Overall (Day1 – 5) CR
  - Secondary endpoints: Overall complete control (CC), Acute CR and CC, delayed CR and CC
  - Subgroup analysis of Chemotherapy regimen (AC, MEC), Age category (≥60 or <60), Sex, Alcohol drinking habit(YES,NO), and PS (0, 1 or more) were pre-planned.
- The pooled risk difference of DEX compared to Placebo for CR was 16% (95% CI, 13% to 19%) for acute phase and 16% for delayed phase (Ioannidis JCO 2000).
  - **-8%** (half of the 16% risk difference) **is a reasonable statistical non-inferiority margin** in the comparison between 3-day DEX regimen and DEX-sparing regimen.
- Common risk difference was estimated through a fixed effect model. Heterogeneity were assessed using treatment-by-trial interaction model and I^2 statistics.

RESULTS

Figure 2: Flow diagram (all IPD could be obtained)

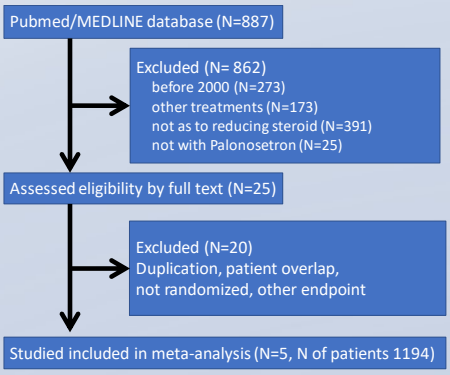

Figure 3: Forest plot for CR overall

- Common risk difference was **-2% (95% CI; -7% to 4%; P = 0.590)**. The lower 95%CI is above of the non-inferiority margin -8% and non-inferiority was shown.

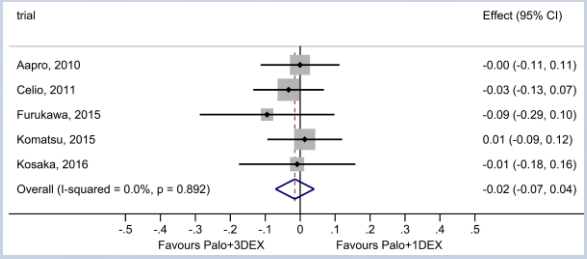

Figure 4: Forest plot for CR delayed phase (Day2-5)

- Common risk difference was **-2% (95% CI; -7% to 3%; P = 0.387)**. The lower 95%CI is above of the non-inferiority margin -8% and non-inferiority was shown.

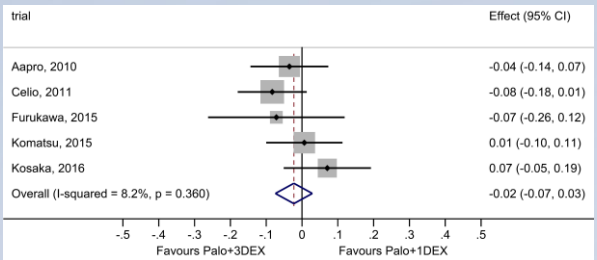

Table 1: Subgroup analysis for CR overall and interaction

	subgroup	N	risk difference [95% CI], %		Interaction P
Sex	Man	289	-2.2%	[-12.3, 7.9]	0.920
	Woman	805	-1.8%	[-8.3, 4.8]	
Age	<60	574	-4.7%	[-12.6, 3.2]	0.196
	≥60	520	2.2%	[-5.5, 9.8]	
Chemo-therapy	AC	467	-2.5%	[-11.0, 6.1]	0.800
	MEC	627	-1.0%	[-8.3, 6.2]	
Alcohol	YES	295	-6.5%	[-16.7, 3.7]	0.283
	NO	730	-0.7%	[-7.6, 6.1]	

CONCLUSIONS

These results strongly suggest that the dexamethasone-sparing regimen is not associated with a significant loss in overall antiemetic control in an adult patient undergoing MEC or AC-containing chemotherapy, irrespective of patient baseline characteristics. These data contribute to simplify antiemetic regimens and spare many patients from the potential side-effects of multiple-day corticosteroids.

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