ONLINE RESOURCE: SUPPLEMENTARY DATA

JOURNAL: Supportive Care in Cancer

TITLE: Efficacy and tolerability of transdermal granisetron for the control of chemotherapy-induced nausea and vomiting associated with moderately and highly emetogenic multi-day chemotherapy: a randomized, double-blind, Phase III study

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Section 1: Methods

Classification of emetogenicity

An emetogenicity classification was devised based on the single-agent Hesketh levels[1]. For each single day, the emetogenicity was calculated by identifying the Hesketh score of the most emetogenic agent and adding the remaining agents to this score, according to the following system: level 1 agents did not contribute to the score; adding one or more level 2 agents increased the score by 1; adding level 3 or 4 agents increased the score by 1 per agent (Table S1). The highest score on any of the 3–5 days of a regimen defined its overall emetogenicity. MEC and HEC regimens were defined as those with overall emetogenicity levels of 3–4 and >4, respectively, for a 3–5-day period.

Table S1: Calculation of emetogenicity score based on single-agent Hesketh levels

1. Identify the agent with the highest emetogenicity score.
2. Determine the contribution of the remaining agents:

	Examples			
i. Level 1 agents do not contribute to emetogenicity	Level 1+1=0	2+1=2	3+1=3	4+1=4
ii. Adding 1 or more level 2 agents increases the score by 1	Level 2+2=3	3+4=4	2+2+2=3	3+2+2=4
iii. Adding 1 or more level 3 agents increases the score by 1 per agent	Level 3+3=4	3+3+3=5	4+3=5	

3. The highest score on any day of a regimen defines the overall emetogenicity of a multi-day regimen.

Example: Breast cancer, 3-day regimen

Day 1	Day 2	Day 3
fluorouracil, epirubicin, cyclophosphamide (FEC)	FEC	FEC
= 2+3+4	= 2+3+4	= 2+3+4
= 5	= 5	= 5

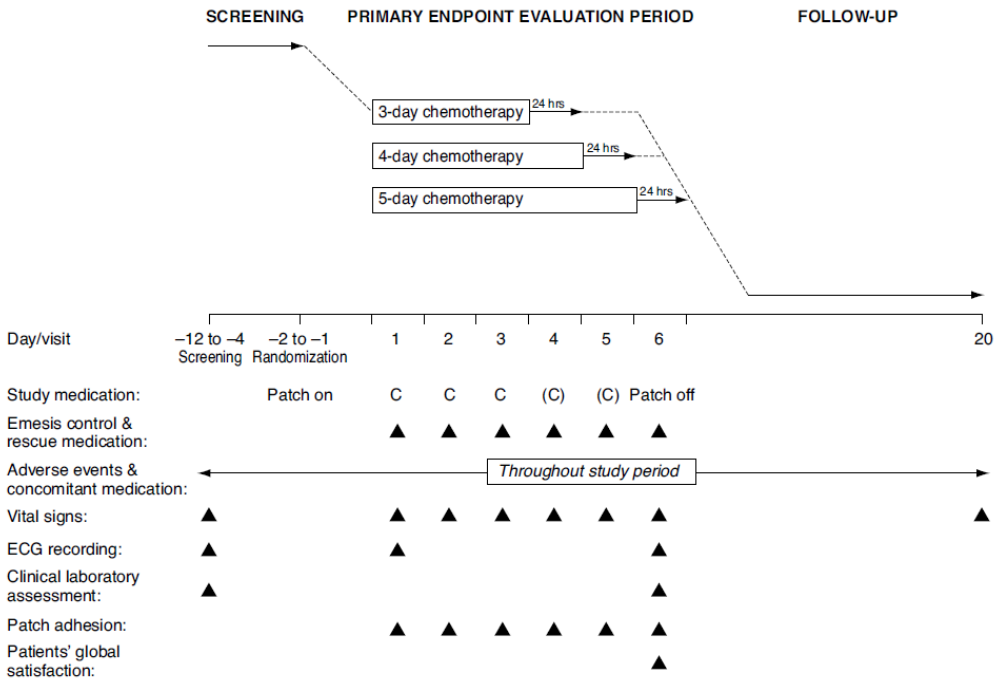
Overall emetogenicity score = 5, highly emetogenic

Study design, visits and evaluations

Following a 7-day screening period, patients were randomized to receive oral granisetron with a placebo patch or the GTDS with placebo capsules. Patches were applied to the upper arm 24–48 hours before the start of chemotherapy, by the investigator or the patient, and left in place for 7 days. Capsules were administered 1 hour before each day's administration of chemotherapy (Figure S1). The primary efficacy endpoint was evaluated between the first administration of chemotherapy and 24 hours after the last administration (the primary endpoint evaluation period, PEEP; Figure S1).

Fig. S1 Study visits and evaluations

C, capsule administered to all patients at this visit; (C), capsule administered to patients still receiving chemotherapy at this visit; ▲, assessment made at this visit



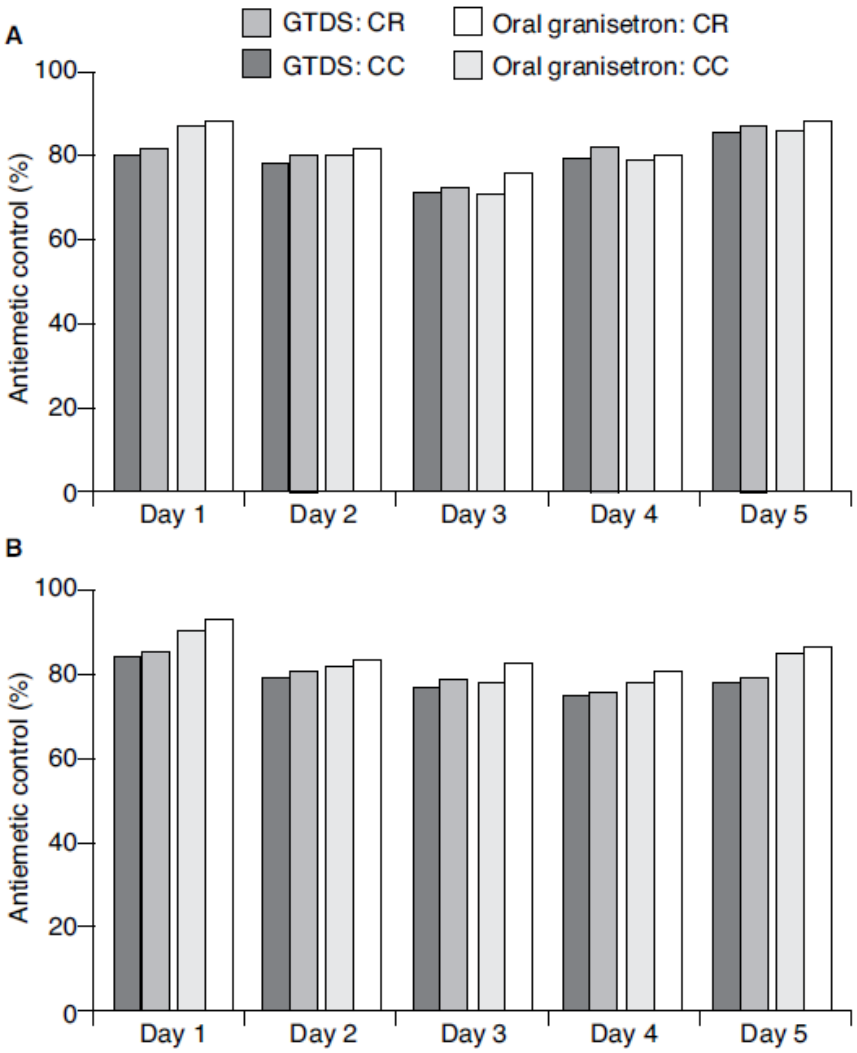
Section 2: Additional secondary efficacy analyses

For those patients who did not achieve CC throughout the PEEP (113 and 105 treatment failures in the GTDS and oral granisetron groups, respectively), the time to CC failure was similar for the two groups. There was no significant difference between the groups in time to failure of CC (hazard ratio 1.2, 95% CI 0.9–1.6, p=0.168). The median time to failure was 28.5 hours (95% CI 20.4–36.6) for the GTDS group, compared to 30.7 hours (26.3–35.1) in the oral group.

In patients receiving 3-day chemotherapy, CC and CR were similar between GTDS and oral granisetron treatment groups on all days of therapy (Figure S2A). Furthermore, for patients receiving 5-day chemotherapy, percentage CC and CR were also similar between treatment groups on all days of chemotherapy (Figure S2B).

Fig. S2 Antiemetic control for patients receiving 3-day (A) and 5-day (B) chemotherapy regimens in the full analysis set

CC, complete control; CR, complete response



The number of patients (GTDS vs oral granisetron, respectively) who failed the composite endpoint of TC through the use of rescue medication (9 vs 5), nausea (77 vs 79) or vomiting (50 vs 40) was very similar between the two treatments (for patients failing through multiple events, the investigator judged the predominant event while still blinded to the treatment).

Section 3: Discussion of exploratory subgroup analyses

Through the exploratory subgroup analyses, the efficacy of the GTDS was consistently demonstrated across a range of patient groups, including those with known CINV risk factors. The results showed that the GTDS was effective against both MEC and HEC, regardless of its duration or the inclusion of cisplatin and corticosteroids in the regimen. In some patient groups, including chemotherapy-naïve patients and patients receiving 4-day chemotherapy regimens, large point differences between the treatments were apparent. However, these groups also displayed wide 95% confidence intervals, reflecting small patient numbers and a diversity of patients within the groups. Importantly, none of the subgroups showed a significant difference between treatments at this confidence level.

References

1. Hesketh PJ, Kris MG, Grunberg SM, Beck T, Hainsworth JD, Harker G, Aapro MS, Gandara D, Lindley CM (1997) Proposal for classifying the acute emetogenicity of cancer chemotherapy. J Clin Oncol 15:103-109