2. Cancer (Condition after Cancer Surgery and Unspecified Adverse Drug Reactions of Anti-cancer Drugs)

Reference

Oki E, Emi Y, Kojima H, et al. Preventive effect of Goshajinkigan on peripheral neurotoxicity of FOLFOX therapy (GENIUS trial): a placebo-controlled, double-blind, randomized phase III study. *International Journal of Clinical Oncology* 2015; 20: 767-75.

1. Objectives

To evaluate the preventive effect of goshajinkigan (牛車腎気丸) for FOLFOX-induced peripheral neurotoxicity.

2. Design

Double-blind, randomized controlled trial (DB-RCT).

3. Setting

Multiple centers, Japan.

4. Participants

One hundred and eighty-six colon cancer patients receiving mFOLFOX6 as adjuvant chemotherapy after surgery.

5. Intervention

Arm 1: TSUMURA Goshajinkigan (牛車腎気丸) Extract Granules 7.5 g/day (2.5g t.i.d. before meals or between meals) taken orally from mFOLFOX start date until the end of the 12-cycle regimen (n=93).

Arm 2: Placebo (Yamato Logistics Co., Ltd.) taken orally for the same period as above (n=93).

6. Main outcome measures

Primary endpoints: Time until onset of peripheral neuropathy (NCI CTCAE ver.3.0 grade 2 or higher) (time to neuropathy: TTN); Secondary endpoints: Rate of discontinuation of treatment due to peripheral neuropathy, oxaliplatin (L-OHP) relative dose intensity.

7. Main results

In arm 1, 89 participants were analyzed after 4 dropped out. The peripheral neuropathy (grade 2 or higher) incidence rate was 50.6% in the goshajinkigan group (arm 1) which was higher than the placebo group (arm 2) rate of 31.2%. The TTN curve also showed significantly shorter times for the goshajinkigan group (P=0.007, HR=1.908 [1.181-3.083]). Goshajinkigan did not demonstrate preventive effect against grade 1 peripheral neuropathy. No between-group difference was observed for adverse events other than neurotoxicity. The secondary endpoint, L-OHP relative dose intensity, was 78.99% in the placebo group and 83.41% in the goshajinkigan group, which was significantly higher (P=0.033). The rate of discontinuation of treatment was not mentioned.

8. Conclusion

Goshajinkigan indicated a preventive effect against FOLFOX-induced peripheral neuropathy.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No significant between-group difference was observed for hematotoxicity or non-hematotoxicity.

11. Abstractor's comments

This is an important study that sought to verify for the first time in a phase III double-blind, placebo-controlled trial of the preventive effect of goshajinkigan for FOLFOX-induced peripheral neuropathy in colon cancer patients. But as a result of interim analysis at 142 participants out of the target 310, there were more cases of peripheral neuropathy in the goshajinkigan group, and the independent monitoring committee recommended discontinuation. The trial was discontinued at 186 registered participants. The authors surmise that chronic/accumulative peripheral neuropathy cases increased due to larger doses of L-OHP in the goshajinkigan group. However, it seems that it was the only possible cause of the results in this study. The paper mentions that overall survival time and recurrence-free survival time would be investigated after 5 years. If there would be survival benefit in the goshajinkigan group, conducting this RCT would have significance. Furthermore, the ingredients with a neuroprotective action reach their highest blood concentration about at 60 minutes after administration of goshajinkigan. It is difficult to understand what the authors mean by their consideration that the timing of goshajinkigan administration might be related to prevention of chronic peripheral neuropathy and L-OHP relative dose intensity.

12. Abstractor and date

Motoo Y, 27 December 2016.