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

Reference

Toda T, Matsuzaki K, Kawano T, et al. Preoperative and postoperative combination therapy with slow-release tegafur capsules and Juzen-taiho-to in patients with colorectal cancer - Tissue concentrations and thymidine phosphorylase activity -. *Gan no Rinsho* (*Japanese Journal of Cancer Clinics*) 1998; 44: 317-23 (in Japanese with English abstract). MOL, MOL-Lib

1. Objectives

To elucidate the mechanism by which juzentaihoto (十全大補湯) reduces the adverse reaction to treatment with 5-fluorouracil (5-FU) (hepatopathy) by determining the distribution of 5-FU in tissues of patients with colorectal cancer receiving slow-release tegafur preoperatively.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

One hospital, Japan.

4. Participants

Forty-four patients with colorectal cancer who received the anti-cancer drug tegafur (slow-release capsules, 800 mg/day) preoperatively and postoperatively.

5. Intervention

Arm 1: combination of juzentaihoto (十全大補湯) (manufacturer unknown) 7.5 g/day with slow-release tegafur capsules for 7–20 days preoperatively (n=24).

Arm 2: administration of slow-release tegafur capsules alone for 7–20 days preoperatively (n=20).

As postoperative adjuvant chemotherapy, the treatment was continued as long as possible in both arms.

6. Main outcome measures

Tegafur and 5-FU concentrations in peripheral blood, tegafur and 5-FU concentrations and thymidine phosphorylase (TP) activity in surgical specimen tissues (tumor and normal tissues), amount of tegafur converted to 5-FU per TP activity unit in tumor and normal tissues, tumor/normal tissue ratio of the amount of tegafur converted to 5-FU per TP activity unit, hematology/liver function test/total protein at start and completion of administration.

7. Main results

The 5-FU concentration in non-tumor tissues was higher in arm 2 than in arm 1 ($P<0.05$). There were no significant between-arm differences in tegafur and 5-FU concentrations in peripheral blood and tumor tissue, or in tegafur concentration in normal tissues. The common adverse drug reactions to slow-release tegafur (anorexia, nausea/vomiting, and diarrhea) occurred later in arm 2 (9/23) than in arm 1 (6/28). The change in glutamic pyruvic transaminase (GPT) between the start and completion of administration was not significant in arm 1 but it was significant in arm 2 ($P<0.01$), suggesting that juzentaihoto may suppress development of liver dysfunction. Thymidine phosphorylase (TP) activity was higher in tumor tissues than in normal tissues both in arm 1 ($P<0.01$) and arm 2 ($P<0.05$). Conversion of tegafur to 5-FU per TP activity unit was higher in tumor tissues than in normal tissues in arm 1. The ratio of the conversion to 5-FU per TP activity unit in tumor tissue to that in normal tissue was higher in arm 1 than in arm 2 ($P<0.05$).

8. Conclusions

Administration of juzentaihoto in patients receiving slow-release tegafur capsules increases 5-FU concentration in tumor tissues but decreases 5-FU concentration in normal tissues, enhancing the tumor selectivity of tegafur. This effect may be partly due to the modulation by juzentaihoto of TP activity in tissues and of cytochrome P-450 (CYP).

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

It is attractive to suppose that a Kampo medicine modulates the effect of a drug-metabolizing enzyme to increase the tumor selectivity of an anti-cancer drug. Identification of the active component(s) of the Kampo medicine may pave the way for development of novel anti-cancer drugs. However, given the large standard error of the mean (SEM), it is unreasonable to conclude from higher GPT values at the completion of treatment that juzentaihoto suppresses hepatopathy associated with slow-release tegafur capsules. It would be more reasonable to attribute the higher GPT values to discontinuation of treatment in a few patients who developed hepatopathy.

12. Abstractor and date

Hoshino E, 26 April 2009, 6 January 2010, 1 June 2010, 31 December 2013.