Adjuvant S-1 chemotherapy after curative resection of gastric cancer

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To the Editor—In the February issue of *Hong Kong Medical Journal*, Yeo et al[1] reported an informative study on the use of S-1 as adjunct chemotherapy after curative resection of gastric cancer.

Since the active ingredient in S-1 is the prodrug tegafur, to be converted to 5-fluorouracil (5FU), much of the toxicity reduction depends on the degradation of 5FU by dihydropyrimidine dehydrogenase (DPD) encoded by the *DPYD* gene. Loss-of-function mutations in *DPYD* would lead to excessive toxicity and, on rare occasions, could be fatal. This applies also to prodrugs such as capecitabine.[2] The incidence of *DPYD* variants leading to reduced DPD activity has been estimated to be 3% to 5% in a western population and complete loss of function at 0.2%.[3] A Korean study showed that minor allele frequency of single nucleotide polymorphism varies across different ethnic groups, being lowest in Koreans, followed closely by Chinese and Japanese with Caucasians having a higher level.[4]

For the 3% to 5% of patients with reduced DPD activity, S-1 (tegafur/gimeracil/oteracil) has the built-in safety factor similar to an earlier tegafur combination UFT (tegafur/uracil). With UFT, tegafur gives a level of 5FU below the conventional therapeutic level. Yet efficacy is achieved by uracil, another component of UFT, which reduces the activity of DPD and results in partial DPD deficiency. A study has revealed that patients with partial DPD deficiency (due to heterozygotic *DPYD* mutations) could be treated successfully by UFT.[5] Presumably S-1 could be used similarly.

For the 0.2% of cases with homozygous defects in *DPYD*, perhaps Prof Yeo and her colleagues have already provided the answer in their paper when they quoted a Taiwan study in which a single-dose pharmacokinetic study tested the tolerability of S-1 in the individual patient.[6] Using a small dose may appear contrary to traditional oncology practice, but in this particular situation it could be a practical and cost-effective way to avoid some alarming outcomes.

I declare no conflicts of interest other than having also used small single doses of 5FU and have screened out two patients with very severe toxicity over the past 30 years.

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Authors' reply

To the Editor—We thank Dr Leung for his comments. Fluoropyrimidine-associated toxicity occurs in approximately 30% of the patients who are being treated, and is fatal in 0.5% to 1%.[1]

While the 2016 'ESMO consensus guidelines for the management of patients with metastatic colorectal cancer' recommends that "DPD testing before 5-FU administration remains an option but is not routinely recommended",[2] others have raised concern based on cumulative data over the past 30 years that show DPD deficiency is strongly associated with severe and fatal fluoropyrimidine-induced toxicity.[3] In particular, a recent meta-analysis provides robust data that show four *DPYD* variants, namely DPYD*2A, c.2846A > T, c.1679T > G, and c.1236G > A/Haplotype B3 to be associated with fluoropyrimidine toxicity.[4]

It has to be noted that apart from 5FU, other fluoropyrimidine compounds include capecitabine, UFT, and S1. Although plasma 5FU concentrations following capecitabine administration can be more affected by DPD, they vary less extensively following administration of DPD-inhibitory fluoropyrimidines,

S-1, and UFT.[5] Studies have suggested that S-1 can be safely administered to cancer patients with DPD deficiency because DPD is already inactivated by gimeracil (CDHP) when S-1 is administered.[6] Severe toxicities, however, can still be associated with different fluoropyrimidines and hence further research on the biomarkers of chemotherapy sensitivity and toxicity is needed.

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