



Treatment improvement by addition of leucovorin to S-1 plus oxaliplatin in patients with advanced gastric cancer

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Regional differences in gastric cancer are observed between Asian and Western countries concerning prevalence, clinicopathologic features, as well as treatment strategies. Cisplatin and fluoropyrimidine based therapies are used as backbone of first-line chemotherapy for advanced gastric cancer treatment, although there is preference for 5-fluorouracil (5FU) or capecitabine in the West while S-1 is mostly used in Asia. REAL-2 and Al-Batran *et al.* studies have shown that oxaliplatin was as effective as cisplatin in combination with capecitabine or 5FU in Western countries (1,2). In the same way, in Asian countries, Yamada *et al.* have demonstrated recently that oxaliplatin could replace cisplatin in combination with S-1 for gastric cancer in first-line treatment with favorable safety profile (3). A third agent (docetaxel or epirubicin) may be added (more commonly in Western countries) for patients with good performance status (1,4).

Several data demonstrated that leucovorin was able to improve the efficacy of fluorouracil by stabilising the ternary complex formed between fluorodeoxyuridine monophosphate (FdUMP) and thymidylate synthase (5), whereas adding leucovorin to capecitabine provided little additional benefit and more adverse events (6). S-1 is an oral fluorouracil antitumor drug that combines tegafur (prodrug of 5FU), 5-chloro-2,4-dihydroxypyridine (which inhibits dihydropyrimidine dehydrogenase activity) and potassium oxonate (which reduces gastrointestinal toxicity) (7). In advanced colorectal cancer, increasing evidence indicates that addition of leucovorin to S-1 might improve its

efficacy (8,9). Likewise, the addition of leucovorin to S-1 in gastric cancer treatment is equally expected to enhance the antitumor activity. However, no data have been reported yet in gastric cancer patients.

Recently, Hironaka and colleagues have evaluated in a randomized phase II study the activity and safety of S-1 plus leucovorin (n=49), versus S-1 plus leucovorin and oxaliplatin (n=47), versus S-1 plus cisplatin (n=49), as first-line chemotherapy in Japanese patients with advanced gastric cancer (7). In this study, the objective response rate (ORR), which was the primary endpoint, was higher in the S-1 plus leucovorin and oxaliplatin group (66%) compared to S-1 plus leucovorin (43%) (Fisher's exact test: P=0.038) or S-1 plus cisplatin groups (46%) (Fisher's exact test: P=0.063). The median progression-free survival was longer in the S-1 plus leucovorin and oxaliplatin group (8.3 months) compared to S-1 plus leucovorin (4.2 months; HR: 0.52, P=0.013) or S-1 plus cisplatin groups (5.6 months; HR: 0.60, P=0.054). The median overall survival was also longer in the S-1 plus leucovorin and oxaliplatin group (18.4 months) compared to S-1 plus leucovorin (15.6 months; HR: 0.76, P=0.27) or S-1 plus cisplatin groups (12.6 months; HR: 0.59, P=0.023) (7). This study suggests firstly that (I) addition of oxaliplatin to S-1 plus leucovorin improves efficacy of chemotherapy; and secondly that (II) S-1 plus leucovorin and oxaliplatin is more effective than S-1 plus cisplatin treatment. Haematological grade 3–4 toxicities were more frequent in the S-1 plus cisplatin group (neutropenia, anaemia, and leucopenia), while non-haematological toxic

effects, such as decreased appetite and diarrhea, were more common in the S-1 plus leucovorin and oxaliplatin group (7).

Based on these results and data from previous phase III study showing that S-1 plus oxaliplatin was non inferior than S-1 plus cisplatin in terms of survival (3), it can be extrapolated that leucovorin might provide an additional benefit when combined with S-1 plus oxaliplatin. However, in our opinion, it is difficult to definitely conclude on leucovorin's benefit as the S-1 plus oxaliplatin without leucovorin arm is missing in the present study. In fact, the only way to answer this question would have been to randomize patients to receive S-1 (alone or combined with oxaliplatin) with or without leucovorin.

In view of these findings, a phase III trial comparing S-1 plus leucovorin and oxaliplatin versus S-1 plus cisplatin in patients with HER2-negative gastric cancer is planned in Japan and Korea (NCT02322593). The supposed standard arm in this ongoing study is S-1 plus cisplatin. In our opinion, the real question is whether leucovorin could improve efficacy of S-1 plus oxaliplatin, since oxaliplatin is already a validated option in combination with 5FU or S-1 for advanced gastric cancer patients (2,3). If we consider that S-1 plus oxaliplatin is as effective as S-1 plus cisplatin, one could have considered S-1 plus oxaliplatin as the standard arm instead of S-1 plus cisplatin which was associated with more grade 3–4 toxicities in a previous randomized phase III study (neutropenia, anemia, hyponatremia and febrile neutropenia) (3). Furthermore, to our knowledge, there is no data concerning the potentiation of antitumor activity with the addition of leucovorin to S-1 plus cisplatin. Thus, we can suppose that the better clinical outcomes observed in S-1 plus leucovorin and oxaliplatin compared to S-1 plus cisplatin is mainly due to the addition of leucovorin to S-1 in oxaliplatin-based treatment arm, but not a superiority of oxaliplatin versus cisplatin. Another option would have been thus to ask both questions in a factorial design randomizing oxaliplatin versus cisplatin and leucovorin versus without leucovorin.

In conclusion, treatment and types of chemotherapy used in advanced gastric cancer vary according to geographic regions. Combination of fluoropyrimidine (including oral capecitabine or S-1) with a platinum salts (cisplatin or oxaliplatin) remains the most widely accepted reference regimen. In Asian countries, S-1 has been widely developed and is currently used as a standard first-line chemotherapy in combination with platinum. Preliminary studies have shown that addition of leucovorin to S-1 demonstrated promising synergic effect with acceptable toxicity that

needs to be confirmed in phase III randomized study. Likewise, there is a variation in clinical outcomes for gastric cancer patients across worldwide. This could be explained by difference in treatment strategies, tumor biology, and also in mutations or polymorphism in genes regulating oncogenic signaling pathways or involved in anti-tumor drug metabolism and pharmacokinetics, such as dihydropyrimidine dehydrogenase or thymidylate synthase for fluoropyrimidine. The ultimate goal in the future will be to personalize treatment according to the patient's genetic profile and tumor biology in order to select the most effective and safe treatment for each patient.

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