EUR. J. ONCOL., vol. 19, Suppl n. 1, pp. 26-29, 2014

S-1 in the treatment of advanced gastric cancer: up-date

Rosa Laface, Elisa Giommoni, Francesco Di Costanzo
Medical Oncology Unit, Dpt of Oncology, Azienda Ospedaliero Universitaria Careggi, Florence, Italy

Introduction

Despite a marked decline in the incidence during last decade, stomach cancer remains the third most prevalent malignancy in the world. More than 70% of cases are diagnosed in developing countries, and approximately half the world's total number of cases occurs in Eastern Asia (mainly in China). In Europe approximately 95.000 new cases are diagnosed every year and 75.000 die due to it. Advanced disease represents more than two-thirds of newly diagnosed gastric cancers when the tumor is unresectable. At diagnosis, 30% of gastric cancer is locally advanced and another 30% is metastatic. Pts with unresectable disease (advanced or metastatic disease) have a poor prognosis, with an overall 5-year survival in various series within the range of 5%-15%. Then, sixty percent of resected pts relapses after surgery, and globally 80-84% of them will have advanced disease (2-3). The prognosis of metastatic and locally AGC is different, median overall survival (mOS) is 7-10 months (mos) and 12-15 mos , respectively (1-3).

Wagner et al, in a meta-analysis, performed a sub-analysis of 11 randomized studies that compared single agent versus the combination, reported an HR of 0.83 (95% CI: 0.74-0.93) for OS in favour of association CT. The combination containing cisplatin (P) is superior to schedules without it. The additional benefit of Epirubicin remains questionable, as the use of combination of two or three drugs is still open. Other combinations, combining epirubicin, oxaliplatin (OXA), and capecitabine or docetaxel, P, and 5-Fluorouracil (5-FU), have claimed efficacy similar to or better than that of epirubicin, P, and 5-FU (4).

S-1 is a novel oral fluoropyrimidine that has demonstrated antitumor activity against AGC when used either as a single agent or in combination with other chemotherapies(5). This review will focus on the oral fluoropyrimidine S-1in the treatment of advanced gastric cancer.

S-1

S-(Teysuno™) is an an oral fixed-dose combination of three active substances: 5-FU prodrug called tegafur and the two enzyme inhibitors 5-chloro-2,4-dihydroxypyridine (CDHP) and oteracil potassium (Oxo), in a molar ratio of 1:0.4:1. Following oral ingestion, tegafur is gradually converted to 5-FU in the liver through hydroxylation, mainly by cytochrome P450 2A6 enzyme (CYP2A6) activity in the liver. 5-FU is activated within cells by phosphorylation of its active metabolite, 5-fluoro-2'-deoxyuridine-monophosphate (FdUMP). The oral 5-FU formulation would allow for sustained 5-FU plasma concentrations, mimicking the pharmacokinetics (PK) of a continuous infusion with the addition of convenience of administration. Gimeracil (CDHP) inhibits the activity of dihydropyrimidine dehydrogenase, thereby allowing 5-FU to remain in high concentrations for a longer time in serum and tumor tissue. Oteracil (Oxo) is distributed in the gastrointestinal tract at a high concentration following oral administration, and it prevents phosphorylation of 5-FU by inhibiting the effect of orotate phosphoribosyl transferase(6). The effect of tegafur and gimeracil was greatest when both substances were administered simultaneously. Myelos-

uppression was the principal toxicity that has precluded dose escalation in Japanese studies, whereas gastrointestinal and skin toxicity were the features of western trials. In addition, anemia was the unique toxicity encountered in a Korean phase II study (14 Jeung HC). Regardless, maximum tolerated doses were found to be higher in Asian studies than in western studies, and Korean study obtained the highest dose intensity ever reported with favorable compliance (14, 26 Chu QSC). This is partially explained by aforementioned ethnic variation in the cytochrome P450. In American and European studies, diarrhea is the major toxicity that causes dose reductions, suggesting that some kind of ethnic differences may contribute to treatment outcome and safety. In vivo, during repeat-dose toxicology studies in the dog, S-1 and FCD induced melanosis in the sclera, conjunctiva, skin, and lymph nodes. Repeat dosing of S-1 was associated with skin and eye toxicity in the rat and dog. The tegafur component of S-1 appeared to be responsible for the melanin deposition and eye toxicity. Coadministration of warfarin and S-1 increase the risk of bleeding. Fluoropyrimidines may increase the plasma concentretion of phenynthoin when administered concomitantly. Allopurinol may decrease activity of S-1 by suppression of phosphorylation of 5-FU (7).

Clinical Trials

In the 1990s, S-1 (TS-1; Taiho Pharmaceutical, Tokyo, Japan), was developed for the treatment of gastric cance . With an exceptionally high response rate of 45-54% similar to efficacy obtained in Western trials with others combination drugs (8-9). This drug quickly became the standard treatmen for AGC in Japan and was used widely in clinical practice. A phase III trials proved the non-inferiority of S-1 when compared with infusional 5-FU in the advanced/metastatic setting (10), along with the superiority of S-1 monotherapy over observation alone in the postoperative adjuvant setting (11). Boku et al (JCOG9912-trial) planned a three-arm phase III study to evaluate the single agent 5FU vs the combination CPT11 plus CDDP (P) vs S-1 alone. Two-hundred thirty pts were enrolled per arm and the results showed a significant non-inferiority of S-1 vs 5-FU ($p \leq 0.001$) However, either S-1 or Irinotecan plus P failed to show superiority to 5FU ($p \leq 0.034$ and 0.055 respectively) in OS(10). Phase II/III studies have been performed to explore combinations of S-1 with other cytotoxic drugs such as P (12), docetaxel (13), paclitaxel and irinotecan (14). All these combinations were found to be promising, with response rates of around 50% and relatively favorable safety profiles

Recently, Takiuchi et al. reported promising results with the combination of OXA plus S-1 in first line therapy. The overall response rate (ORR) was 58.8% (95% CI: 44.2-72.4%) and clinical benefit was 84.3% (95% CI: 71.4-93.0) with a median PFS of 6.5 mos (95% CI:4.8-11.3 mos) and median TTF of 4.8 mos (95% CI: 4.0-5.6 mos). Grade 3-4 major adverse reactions were neutropenia (22%), thrombocytopenia (13%) (15).

S-1, when combined with docetaxel and P in a phase II trial including 59 pts, reported a high ORR of 81.3% (48/59; 95% CI: 80.7-91.2). Grade 3-4 major toxicity included leucopenia (44.0%), neutropenia (72.8%), anemia (15.2%) febrile neutropenia (13.5%) with one treatment related death caused by the perforation of primary tumor (16).

A Japanese trial (SPIRT trial) evaluated in a phase III trial the combination of S-1 and P compared with S-1 in 305 pts with AGC. The primary end point was overall survival (OS). In this study 148 naive pts with AGC received S-1 plus CDDP and 150 pts S-1 alone. Median OS was significantly longer in the S-1 plus P arm (13.0 vs 11.0 mos; $p<0.04$). Also, PFS was longer in the combination arm, with a median PFS of 6.0 mos vs 4.0 mos ($p<0.0001$). The ORR, registered in 87 pts alone, was 54% (range 43-65%) in the arm using S1 plus CDDP; one pt had complete response (CR) and 46 pts had partial response (PR), while 106 pts assigned to S1 alone had ORR 31% (range 23-41%), with one CR and 3 PR. Grade 3-4 adverse events, including leucopenia, neutropenia, anemia, nausea and anorexia were more frequent in the CDDP combination. No treatment-related deaths were reported in either group (17). First Line Advanced Gastric Cancer Study (FLAGS), an open label, multicenter randomized trial, enrolled 1053 (S-1 plus

P, n = 521; 5-FU plus P, n = 508) with AGC pts in 147 sites in 24 countries, to evaluate if S-1 plus CDDP (PS) was better than 5FU plus CDDP (PF). The primary analysis showed that PS and PF had a similar OS for non-inferiority. In the stratification analysis (unplanned) PS resulted in a superior median OS than PF in diffuse type histology (9.0 vs 7.1 mos; p=0.0413; HR 0.83 (95% CI: 0.70-0.99)) and in North American pts. PS also had a better safety profile. Significant safety advantages were observed in the PS arm compared with the PF arm for the rates of grade 3/4 neutropenia (32.3% v 63.6%), complicated neutropenia (5.0% v 14.4%), stomatitis (1.3% v 13.6%), hypokalemia (3.6% v 10.8%), and treatment-related deaths (2.5% v 4.9%; P< .05). PS did not prolong OS of pts with AGC or gastroesophageal adenocarcinoma compared with PF, but it did result in a significantly improved safety profile. The FLAGS study was designed and conducted as a superiority study. However, after the primary analysis failed to show superiority of S-1 plus P over PF, the end point hypothesis was switched from superiority to non-inferiority . This point was considered a major methodological bias in FLAGS trial (18).

S-1 plus P has become a standard treatment for advanced gastric cancer in East Asia. However, P has several disadvantages, including renal toxicity. START Trial, a phase III study, was designed to evaluate the potential benefits of adding docetaxel to S-1 without a platinum compound in pts with advanced gastric cancer. The primary end point was OS. The mOS was 12.5 mos in the docetaxel plus S-1 group and 10.8 mos in the S-1 alone group (p=0.032). The median progression-free survival (PFS) was 5.3 mos in the docetaxel plus S-1 group and 4.2 mos in the S-1 alone group (p=0.001). As for adverse events, neutropenia was more frequent in the docetaxel plus S-1 group, but remained manageable. As first-line treatment for AGC, docetaxel plus S-1 significantly improves median overall and progression-free survival as compared with S-1 alone (19).

The trial GC0301/TOP-002 randomized S-1 alone vs Irinotecan plus S-1(IRI-S) to evaluated as primary end point OS. The mOS for S-1 was 10.6 (95% CI:286-395 days) vs 12.9 mos (95% CI:324-459 days) for IRI-S. The ORR was significantly different: 26.9% and 41.5% (p<0.004) in S-1 and the combination arm respectively, but only 187 pts were evaluated for ORR. Time to treatment failure (TTF) was better in IRI-S arm (138 days) compared to S-1 alone (111 days; p<0.16; HR 8.85). In the S-1 arm, 45.6% of patient received an Irinotecan based regimen after PD and median OS of this group was 496 days (95% CI:395-573). In conclusion, this trial did not show any significant superiority of combination therapy over S-1 alone in terms of OS (20).

In Europe capecitabine plus P (XP) is considered an interesting as a first-line treatment of AGC. XParTS II-trial are evaluating XP versus SP, which is considered standard therapy in Japan. The primary endpoint is progression-free survival and secondary endpoints are OS, TTF, tumor response rate and safety.

Conclusions

Fluoropyrimidine plus P combination is the standard regimen of the first line treatment for advanced gastric cancer. Both S-1 and capecitabine are the prodrug of 5-FU but differ from their process of metabolism. S-1 is an oral chemotherapy for AGC that obtaines an interesting ORR of 45-54% similar to efficacy obtained with combination chemotherapy in advanced gastric cancer. In combination with P, CPT-11 and docetaxel the results are similar to combination with other fluoropyrimidines. New trials, in European pts are needed with S-1 in combination with active drugs for AGC.

References

1. Kelley JR, Duggan JM. Gastric cancer epidemiology and risk factors. J Clin Epidemiol 2003; 56: 1-9.
2. Jemal R, Guilloux A, Oshima A, et al. Incidence and mortality from stomach cancer in Japan, Slovenia and the USA. Int J Cancer 2002; 97: 811-8.
3. Jemal A, Murray T, Ward, *et al*. Cancer Statistics. 2005;CA Cancer J Clin 2005; 55: 10-30.
4. Wagner AD, Grothe W, Haerting J, *et al*. Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. J Clin Oncol 2006; 24 (18): 2903-9.

5. Koizumi W, Kurihara M, Nakano S, Hasegawa K. Phase II study of S-1, a novel oral derivative of 5-FU, in advanced gastric cancer. For the S-1 Cooperative Gastric Cancer Study Group. Oncology 2000; 58: 191-7.
6. Fukushima M, Satake H, Uchida J, *et al*. Preclinical antitumor efficacy of S-1: a new oral formulation of 5-FU on human tumor xenografts. Int J Oncol 1998; 13: 693-8.
7. Sakata Chu QSC, Hammond LA, Schwartz G, *et al*. Phase I and pharmacokinetic study of the oral fluoropyrimidine S-1 on a once-daily-for-28-day schedule in pts with advanced malignancies. Clin Cancer Res 2004; 10: 4913-21
8. Jeung HC, Rha SY, Kim HK, *et al*. Multi-institutional phase II study of S-1 monotherapy in advanced gastric cancer with pharmacokinetics and pharmacogenomic evaluations. Oncologist 2007; 12: 543-54.
9. Y, Ohtsu A, Horikoshi N, Sugimachi K, *et al*. Late phase II study of novel oral fluoropyrimidine anticancer drug S-1 (1 M tegafur-0.4 M gimestat-1 M otastat potassium) in advanced gastric cancer pts. Eur J Cancer 1998; 34: 1715-20.
10. Boku N, Yamamoto S, Fukuda H, *et al*. Fluorouracil versus combination of irinotecan plus P versus S-1 in metastatic gastric cancer: a randomised phase 3 study. Lancet Oncol 2009; 10 (11): 1027-28.
11. Sakuramoto S, Sasako M, Yamaguchi T, *et al*. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med 2007; 357: 1810-20.
12. Ajani JA, Faust J, Ikeda K, et al. Phase I pharmacokinetic study of S-1 plus cisplatin in pts with advanced gastric carcinoma. J Clin Oncol 2005; 23: 6957-65.
13. Fujii M. Chemotherapy for advanced gastric cancer : ongoing phase III study of S-1 alone versus S-1 and Docetaxel combination (JACCRO GC03 study). Int J Clin Oncol 2008; 13: 201-5.
14. Tsuburaya A, Narahara H, Imamura H, *et al*. Updated result on the 2.5-year follow-up of GCO301/TOP-002: Randomized phase III study of irinotecan plus S-1 (IRI-S) versus S-1 alone as first-line treatment for advanced gastric cancer (AGC). J Clin Oncol 2009; 27 (15): Abst 4544.
15. Takiuchi H, Koizumi W, Yamada Y, *et al*. Phase II study of oxaliplatin combined with S-1 (SOX) as first-line therapy for pts with advanced gastric cancer (AGC). J Clin Oncol 2009; 27: 15s, (suppl; abstr 4553).
16. Nakayama N, Koizumi W, Sasaki S, *et al*. Phase II study of combination therapy with docetaxel, cisplatin, and S-1 (DCS) for advanced gastric cancer: (KDOG 0601). J Clin Oncol 2009; 27 (15); Abst 4555.
17. Koizumi W, Narahara H, Hara T, *et al*. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol 2008; 9: 215-21.
18. Ajani JA, Rodriquez W, Bodoky J, *et al*. Multicenter phase III comparision of cisplatin/S-1 (CS) with cisplatin/5-FU (CF) as first line theraphy in pts with advanced gastric cancer (FLAGS): secondary subser analysis. J Clin Oncol 2009; 27 (15): Abst 4511.
19. Koizumi W, Kim YH, Fujii M, *et al*. Addition of docetaxel to S-1 without platinum prolongs survival of patients with advanced gastric cancer: a randomized study (START). J Cancer Res Clin Oncol 2014; 140 (2): 319-28.
20. Narahara H, Iishi H, Imamura H, *et al*. Randomized phase III study comparing the efficacy and safety of irinotecan plus S-1 with S-1 alone as first-line treatment for advanced gastric cancer (study GC0301/TOP-002).Gastric Cancer 2011; 14 (1): 72-80.