



A promising adjuvant chemotherapeutic regimen for resected pancreatic cancer?

Uesaka K, Boku N, Fukutomi A, et al. Adjuvant chemotherapy of S-1 versus gemcitabine for resected pancreatic cancer: a phase 3, open-label, randomised, non-inferiority trial (JASPAC 01). Lancet 2016; 388: 248-57.

Pancreatic adenocarcinoma is usually diagnosed at advanced stage. However, because of widely use of endoscopic ultrasonography and recent advances in radiological examinations, pancreatic cancer can be diagnosed earlier. On the other hand, even the presence of resectability, the success of treatment is not as high as wanted. In 2004, the European Study Group for Pancreatic Cancer-1 (ESPAC-1) trial (1) showed a better survival of the patients who received fluorouracil and folinic acid chemotherapy after resection. The five-year survival rate was 21% among patients who received chemotherapy and 8% among patients who did not. Also in 2007, Oettle et al. (2) (the Charite Onkologie (CONKO)-001 trial) showed that postoperative gemcitabine significantly delayed the development of recurrent disease after complete resection of pancreatic cancer compared with observation alone. Median disease-free survival was 13.4 months in the gemcitabine group and 6.9 months in the control group. Despite of the use of adjuvant chemotherapeutic agents after resection, survival of patients with pancreatic cancer is not still satisfactory. So working on new drugs for pancreatic cancer is still going on.

An article of one of these studies has been recently published in Lancet (3) presented by Uesaka et al. (JASPAC 01 study). After showing that S-1 was an effective chemotherapeutic agent for advanced pancreatic cancer (4) and still being used as a standard adjuvant chemotherapy for the patients with resected gastric cancer in Japan (5), the investigators planned a randomised, open-label, multicentre, non-inferiority phase 3 trial at 33 hospitals joined. S-1 is an oral chemotherapeutic agent containing tegafur (a prodrug of fluorouracil), gimeracil (which inhibits dihydropyrimidine dehydrogenase (DPD) activity and provides high concentration of fluorouracil in blood and tumor tissue) and oteracil potassium (which suppresses

phosphorylation of fluorouracil in gastrointestinal tract and reduces the toxicity of the drug). The investigators targeted to verify the non-inferiority of S-1 to gemcitabine using as an adjuvant chemotherapeutic agent for patients with curatively resected pancreatic cancer who had the histopathological diagnosis of invasive ductal carcinoma. The patients had to have no local residual tumor (R0) or microscopic residual tumor (R1), no cancer cells in intraoperative peritoneal lavage fluid and no distant metastasis or malignant ascites. Patients also had to have adequate oral intake, be older or equal to 20 years old, have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, have no history of chemotherapy or radiotherapy within the past 3 years, to be enrolled within 10 weeks after resection of pancreatic cancer and to have adequate bone marrow, liver and kidney functions. Patients were randomly assigned to either gemcitabine group or S-1 group. After randomization and exclusions, there were 190 patients in gemcitabine group and 187 patients in S-1 group. The primary outcome was overall survival in both treatment groups. The secondary outcomes were the relapse-free survival, incidence of adverse events and health-related quality of life.

As a primary end point, the median overall survival was 25.5 months in gemcitabine group and 46.5 months in S-1 group. The HR for mortality of S-1 compared with gemcitabine was 0.57 (95% CI: 0.44-0.72, p for non inferiority <0.0001 , p for superiority <0.0001). The estimated overall survival was 38.8% for 3 years and 24.4% for 5 years in gemcitabine group whereas were 59.7% and 44.1% for S-1 group, respectively. As one of the secondary end points, the median relapse-free survival was 11.3 months in gemcitabine group and 22.9 months in the S-1 group. The HR for relapse of S-1 compared with gemcitabine was 0.60 (95% CI: 0.47-0.76, $p<0.0001$). The estimated relapse-free survival was 22.6% for 3 years and 16.8% for 5 years in gemcitabine group whereas were 39.2% and 33.3% for S-1 group, respectively. Recurrence occurred in 78% and 66% of patients in gemcitabine and S-1

groups, respectively ($p < 0.0001$). Grade 3 or 4 frequently seen adverse events were similar between two groups as abnormal leucocyte, neutrophil, platelet, haemoglobin levels, anorexia and fatigue. The major difference between two groups was that diarrhoea was more seen in S-1 group. Two grade 5 infections were seen in gemcitabine group (cholangitis in one and pneumonia in one patient). As third of secondary end points, patients of two groups were asked to complete the questionnaire of quality of life. There was no difference between the groups at 6th month, but after all there was an improvement in quality of life in S-1 group.

The investigators suggested that this trial showed not only the non-inferiority, but also the superiority of S-1 to gemcitabine treatment. They discussed on 3 points to explain this superiority of S-1 to gemcitabine. The first point was that S-1 had a higher response rate than gemcitabine in resected patients. This result was similar to results of GEST study (4) which was performed for advanced/metastatic pancreatic cancer patients. The second point was the use of drug during 28 days, and this dose was similar to those of continuously infused fluorouracil. The third point was that S-1 was well tolerated, and when compared to gemcitabine, it could give the chance to clinician to treat the patients without giving up because of adverse events. The major limitation of the trial was that only Japanese patients enrolled to the trial. The pharmacokinetics and pharmacodynamics of S-1 drug were reported to be different between east Asian versus European and North American patients (6). Thus, lower dose of S-1 drug was recommended in European and North American patients when compared to Japanese patients (7).

In conclusion, this Japanese trial showed that S-1 drug was well tolerated and superior to gemcitabine in resected pancreatic cancer patients. However, additional clinical trials are needed to apply the results of the trial to non-east Asian patients. On the other hand, in recent years, combination chemotherapy of gemcitabine plus nab-paclitaxel (8) and FOLFIRINOX (9) showed a survival benefit over gemcitabine alone for metastatic pancreas cancer patients. Now, phase 3

trials of adjuvant chemotherapy using these regimens compared with gemcitabine for resected pancreatic cancer are underway. If these trials show positive results, it will be necessary to compare S-1 with these intensive chemotherapy regimens.

Nilay Danış, Fatih Tekin

Department of Gastroenterology, Ege University School of Medicine, İzmir, Turkey

Received: August 18, 2016

Accepted: August 18, 2016

DOI: 10.5152/tjg.2016.160005

REFERENCES

1. Neoptolemos JP, Stocken DD, Friess H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med* 2004; 350: 1200-10. [\[CrossRef\]](#)
2. Oettle H, Post S, Neuhaus P, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. *JAMA* 2007; 297: 267-77. [\[CrossRef\]](#)
3. Uesaka K, Boku N, Fukutomi A, et al. Adjuvant chemotherapy of S-1 versus gemcitabine for resected pancreatic cancer: a phase 3, open-label, randomised, non-inferiority trial (JASPAC 01). *Lancet* 2016; 388: 248-57. [\[CrossRef\]](#)
4. Ueno H, Ioka T, Ikeda M, et al. Randomized phase III study of gemcitabine plus S-1, S-1 alone, or gemcitabine alone in patients with locally advanced and metastatic pancreatic cancer in Japan and Taiwan: GEST study. *J Clin Oncol* 2013; 31: 1640-8. [\[CrossRef\]](#)
5. 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. [\[CrossRef\]](#)
6. Chuah B, Goh BC, Lee SC, et al. Comparison of the pharmacokinetics and pharmacodynamics of S-1 between Caucasian and East Asian patients. *Cancer Sci* 2011; 102: 478-8. [\[CrossRef\]](#)
7. Hirata K, Horikoshi N, Aiba K, et al. Pharmacokinetic study of S-1, a novel oral fluorouracil antitumor drug. *Clin Cancer Res* 1999; 5: 2000-05.
8. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 2013; 369: 1691-703. [\[CrossRef\]](#)
9. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011; 364: 1817-25. [\[CrossRef\]](#)