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This review summarizes the key podium and poster-discussion presentations pertaining to non-colorectal gastrointestinal malignancies presented at the 43rd Annual American Society of Clinical Oncology Meeting in Chicago, IL.

Gastroesophageal

S-1 is a novel oral fluoropyrimidine that combines tegafur, an oral prodrug of 5FU with a DPD inhibitor (gmeracil) and an inhibitor of 5FU phosphorylation in the GI tract (oteracil). This year, two phase III trials evaluating the efficacy of S-1 in the treatment of advanced gastric cancer were presented. SPIRITS was a multicenter, randomized open-label trial comparing the efficacy and safety of S-1 plus cisplatin versus S-1 alone in first-line advanced gastric cancer (1). Among 298 patients randomized to receive either S-1 40-60mg twice daily for 4 of every 6 weeks or S-1 at the same dose for 3 of every 5 weeks with cisplatin 60mg/m² on day 8, a significant improvement in survival (median: 13.0mos v. 11.0mos/ 1year: 54% vs. 47%, p=0.0366), progression free survival (6.0mos v 5.0mos, p<0.0001) and response rate (54% v 31%) was observed. The Japan Clinical Oncology Group compared the efficacy of 5-FU vs. irinotecan-cisplatin vs. S-1 in the same disease setting (2). In this first-line trial, 704 patients were randomized to one of three 3 treatment arms. Compared to a standard arm of infusional 5FU, S-1 was non-inferior (1 year survival: 48% v 44%) and irinotecan-cisplatin was not superior (1 year survival: 52% v 44%).

So, what is the role of S-1 in the current treatment algorithm for advanced gastric cancer? We now have evidence to support that it is at least as good as infusional 5FU and has meaningful efficacy in combination with cisplatin. While already in wide use in Japan (where capecitabine is not approved), its use in North American remains investigational and studies evaluating its safety and efficacy in the western population are ongoing.



In the neoadjuvant gastric setting, two earlier studies (MAGIC and MRC OEO-2) have already demonstrated a benefit to preoperative chemotherapy (3, 4). A third study was presented this year by the French Intergroup. FFCD9703 was a randomized trial of 2-3 cycles of preoperative cisplatin and 5FU in 224 patients with resectable adenocarcinoma of the stomach and lower esophagus (6). Fifty percent of treated patients went on to receive 1-4 cycles of post-operative chemotherapy. Survival at 5 years was significantly better in the preoperative chemotherapy arm (38% vs. 24%, $p=0.021$). These results supports the findings of the earlier pre-operative studies, and potentially calls into question the added value of epirubicin to a cisplatin-5FU platform.

Pancreas

Regrettably, there was no good news for pancreatic cancer this year. Two highly anticipated phase III trials evaluating the role of biologics in combination with standard chemotherapy were presented. CALGB 80303, previously reported at the ASCO GI symposium in January 2007, compared standard dose gemcitabine to a combination with bevacizumab 10mg/kg q2weeks (6). The results failed to support any improvement in response rate (10% versus 11%), progression free survival (4.7 months versus 4.9 months) or overall survival (median: 6.1 months v. 5.8 months, 1yr: 20% versus 18%). SWOG S0205 was a similar design trial evaluating cetuximab, a monoclonal inhibitor of EGFR which is a commonly activated pathway in pancreatic cancer (7). This study was of particular interest because it follows on the heels of NCIC.PA3 which demonstrated a modest but statistically significant survival benefit with the addition of erlotinib, a small molecule tyrosine kinase inhibitor of EGFR, to gemcitabine (8). A total of 735 chemo-naïve patients were randomized over a two year period. No differences in response rate, progression free survival (3.5 months v. 3.0 months) or survival (median: 6.4 months v. 5.9 months) were observed.

The negative results of these trials were particularly discouraging given their promising single-arm phase II results. This has led to an interest in exploring novel randomized phase II selection and screening designs as a preferred strategy to help prioritize future phase III studies. The need to identify predictive biomarkers is also clearly apparent. Dr. Malcolm Moore reported on the correlative sub-study results of NCIC.PA3 (10). A trend for benefit with erlotinib was observed for tumours with wild-type K-ras compared to mutant K-ras. Survival in the overall cohort was superior for tumours which were EGFR negative (EGFR gene copy analysis by FISH).

Hepatocellular Cancer



On a more positive note, the leading abstract presentation for the ASCO plenary session was by Dr. Josep Llovet reporting on the final results of the phase III trial of sorafenib in advanced hepatocellular carcinoma (SHARP) (11). In this multinational study, 602 previously untreated patients with Child-Pugh A liver function were randomized to sorafenib (an oral multikinase inhibitor) or placebo. A significant prolongation of progression free survival (5.5 months v. 2.8 months, $p=0.000007$) and overall survival (10.7 months v. 7.9 months, $p=0.00058$) was observed. Sorafenib was well tolerated. Given that no standard therapy to-date has been approved for this setting, these favourable results support the use of sorafenib as a standard for the systemic treatment for advanced hepatocellular carcinoma in patients with good hepatic reserve.



References

1. Narahara H, Koizumi W, Hara T, et al. Randomized phase III study of S-1 alone versus S-1 + cisplatin in the treatment for advanced gastric cancer (the SPIRITS trial) SPIRITS: S-1 plus cisplatin vs. S-1 in RCT in the treatment of stomach cancer. Proceedings of ASCO 2007, Abstract 4514.
2. Boku N, Yamamoto S, Shirao K, et al. Randomized phase III study of 5-fluorouracil (5-FU) alone versus combination of irinotecan and cisplatin (CP) versus S-1 alone in advanced gastric cancer (JCOG9912). Proceedings of ASCO 2007. Abstract LBA4513.
3. Cunningham D, Allum WH, Stenning SP et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal carcinoma. N. Engl J Med 2006 Jul 6; 355(1):11-20.
4. Medical Research Council Esophageal Cancer Working Group. Surgical resection with or without preoperative chemotherapy in esophageal cancer: a randomized controlled trial. Lancet 2002;359:1727-33.
5. Boige V, Pignon J, Saint-Aubert P et al. Final results of a randomized trial comparing pre-operative 5-fluorouracil/cisplatin to surgery alone in adenocarcinoma of stomach and lower esophagus: FNLCC ACCORD07-FFCD 9703 trial. Proceedings of ASCO 2007, Abstract 4510.
6. Kindler HL, Niedwiecki D, Hollis D, et al. A double-blind, placebo-controlled, randomized phase III trial of gemcitabine (G) plus bevacizumab (b) versus gemcitabine plus placebo (P) in patients (pts) with advanced pancreatic cancer (PC): a preliminary analysis of Cancer and Leukemia Group B (CALGB) 80303. Proceedings of ASCO 2007. Abstract 4508.
7. Philip PA, Benedetti J, Fenoglio-Preiser C, et al. Phase III study of gemcitabine [G] plus cetuximab [C] versus gemcitabine in patients [pts] with locally advanced or metastatic pancreatic adenocarcinoma [PC]: SWOG S0205 study. Proceedings of ASCO, 2007. Abstract LBA4509.
8. Moore MJ, Goldstein D, Hamm J et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 2007 May 20; 25(15):1960-6.



9. Moore MJ, da Cuna Santos G, Kamel-Reid S et al The relationship of K-ras mutations and EGFR gene copy number to outcome in patients treated with erlotinib on NCIC.PA3. Proceedings of ASCO 2007, Abstract 4521.

10. Llovet J, Ricci S, Mazzaferro V, et al. Sorafenib improves survival in advanced hepatocellular carcinoma (HCC): results of a phase III randomized placebo-controlled trial (SHARP trial). Proceedings of ASCO2007. Abstract LBA1.