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News & Views

American Society of Clinical Oncology's 2008 Gastrointestinal Cancers Symposium (ASCO GI), January 25–27, 2008, Orlando, Florida

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The symposium was cosponsored by ASCO with the American Gastroenterology Association Institute, the American Society for Therapeutic Radiology and Oncology, and the Society of Surgical Oncology.

Combination or sequential approach in colorectal cancer?

Should combination or sequential strategies be preferred in colorectal cancer? This was the subject of an evening debate featured at the ASCO GI meeting.

The controversy had been sparked by studies published recently in the same issue of *The Lancet*. The first – the Focus study (Seymour et al., 2007. *Lancet* 370, 143–152) which compared upfront combination treatment with 5FU (fluorouracil, irinotecan, and oxaliplatin) with sequential therapy – demonstrated that reserving combination therapy for second-line treatment does not compromise patients' survival or quality of life. Second the CAIRO-1 trial (Koopman et al., 2007. *Lancet* 370, 135–142), comparing sequential versus combination strategies with oral capecitabine (Xeloda®), irinotecan (Camptosar®), and oxaliplatin (Eloxatin®), found no significant differences in survival between the two strategies, but showed reduced toxicity rates for patients in the sequential arm.

"In total there have been five trials involving over 4500 patients, none of which showed any benefits in overall survival for first line combination treatment compared with a planned, staged approach," said Professor Matt Seymour (Cancer Research UK Centre, University of Leeds), the principal investigator of the Focus study, adding that the results came several years after the majority of clinicians had embraced combination therapy as standard treatment. "For many oncologists the results make uncomfortable reading because they show that what they've been doing for the last few years is actually

based on a false assumption. Many of their patients would have lived just as long, with fewer side-effects, had they used a sequential approach."

Professor Matt Seymour

One patient group in which there remains a role for the combination strategy, he said, was the metastatic patients with potentially down-stageable disease, who with treatment has the opportunity to become resectable. For this reasons such patients were excluded from the Focus trial. In addition, another group who may benefit from first-line combination treatments are those with major cancer symptoms. "In FOCUS, poor performance-status patients appeared to benefit from the initial combination, although this finding didn't reach statistical significance," said Seymour.

Despite the latest data, Professor Dirk Arnold (Martin-Luther University, Halle-Wittenberg, Germany) believes that

combination therapy should be made available to all patients. It makes intuitive sense, he feels, to hit colorectal cancer “hard and early” with all available drugs, although he conceded that there were no data to support this approach.

Professor Dirk Arnold

Using combination therapy upfront, Arnold argues, allows patients to derive benefit from all the available drugs. He is concerned that patients who do not respond to the initial treatment would be no longer eligible for further treatments, and therefore would miss out on the whole armourmentarium of drugs.

Arnold feels that there is even a role for combination therapy in patients with multiple metasases who would be unlikely to benefit from resection on combination therapy.

“The chance of gaining control of disease is much higher if you start with combination treatment. And once you get control it allows patients to have treatment breaks or de-escalation with withdrawal of toxic drugs,” he said.

Side effects resulting from combination treatment, he said, need to be balanced against the advantage of greater tumour control. “Tumours produce symptoms, and these are often greater than drug side effects,” he said.

Both speakers agreed that personalized medicine using predictive markers offers the way forward. Studies have shown that levels of the tumour marker topoisomerase-1 predict whether patients will benefit from irinotecan or oxaloplatinum, and levels of the RAS oncogene predict whether patients will respond to panitumab.

In a major planned UK Trial, FOCUS-3, Seymour and colleagues will sort patients into four molecular groups using topoisomerase and RAS, with each group then randomized to receive standard or molecularly guided drug treatment.

Wild-type KRAS colorectal tumours respond to panitumumab

Patients with colorectal tumours expressing wild-type KRAS show significantly increased progression free survival with panitumumab (Vectibix), a monoclonal antibody targeting EGFR, while those with mutations in KRAS do not, according to data from a phase III trial reported at ASCO GI (abstract 278).

The study assessed KRAS status in tumour samples from 427 patients with metastatic colorectal cancer taking part in a phase II trial in which they were randomized to panitumumab (6.0 mg/kg every 2 weeks) plus best supportive care or best supportive care alone. Results reported at the meeting showed that 43% of these patients had KRAS mutations.

Patients with tumours expressing wild-type KRAS showed a 55% increase in progression free survival when treated with panitumumab compared to those given best supportive care without the antibody (hazard ratio (HR) 0.45; 95% confidence interval (CI) 0.34–0.59). In contrast, those with mutant KRAS showed no response (HR 0.99; 95% CI 0.73–1.36) ($P < 0.0001$). The median progression free survival was significantly longer, at 12.3 weeks, in patients with wild type KRAS treated with panitumumab than those with mutant KRAS (7.4 weeks). This compared with 7.3 weeks in both KRAS groups treated with best supportive care.

In the group of patients treated with panitumumab, 17% of those with wild type KRAS expressing tumours responded and 34% had stable disease, while 0% of those with mutant KRAS responded and 12% had stable disease.

Reporting the results, Rafael Amado (Amgen Inc., Thousand Oaks, CA, USA) said: “In patients with chemotherapy-refractory metastatic colorectal cancer, the clinical efficacy of panitumumab monotherapy appears to be restricted to patients with wild type KRAS tumours.” He added: “KRAS genotyping of tumours should be strongly considered in patients being treated with panitumumab monotherapy.”

Commenting on the findings, Harpreet Wasan (Hammer-smith Hospital, Imperial College, London, UK), said: “This is the first time that we have a test that really predicts a patient’s chances of not responding to drug treatment, for a cancer other than breast cancer. We have already decided to incorporate KRAS testing in clinical trials in the UK.”

Panitumumab is currently approved in Europe as monotherapy for the treatment of patients with EGFR expressing metastatic colorectal carcinoma with non-mutated (wild-type) KRAS, and after failure of fluoropyrimidine-, oxaloplatin-, and irinotecan-containing chemotherapy regimens. KRAS (Kirsten rat sarcoma 2 viral oncogene homolog) codes for a GTPase involved in signalling cell division. Mutations in KRAS limit KRAS inactivation, impairing self-regulated signal transduction. A commercial test is now available that can be used to assess KRAS status from tumour samples.

Circulating levels of tumour cells predict overall CRC survival

Pretreatment levels of circulating tumour cells (CTC) offers an independent predictor of progression-free survival and overall survival in patients with metastatic colorectal cancer (CRC) regardless of line of therapy, type of therapy or clinical characteristics, concluded a US study reported at ASCO GI (abstract 299).

In the study Neal J. Meropol and colleagues (Fox Chase Cancer Center, Philadelphia, PA, USA) used immunomagnetic separation to measure CTC numbers in 7.5 mL of blood among 430 patients with metastatic colon cancer. Testing was performed before patients started first, second-, or third-line

therapy and at various time points throughout follow-up. For the study patients were then stratified into unfavourable and favourable prognostic groups, with three or more CTCs per 7.5 mL considered to be unfavourable.

Results show that among the 296 patients receiving first-line therapy, median progression-free survival was 6.3 months in the 72 patients with three or more CTCs per 7.5 mL (an unfavourable prognosis) compared with 7.7 months for those with less than three CTCs per 7.5 mL ($P < 0.025$) (a favourable prognosis). Overall all times were 11.6 months in those with an unfavourable prognosis and 21.2 months in those with a favorable prognosis ($P < 0.0001$).

Among the 235 patients who received bevacizumab, median progression-free survival was 6.3 months in the 62 patients who had an unfavourable prognosis compared with 8.6 months for those who had a favourable prognosis ($P < 0.018$). Overall survival was 10.5 months in those with an unfavourable and 18.6 months in those with a favorable prognosis ($P < 0.0005$).

A similar pattern was seen among the 99 patients treated with irinotecan, and the patterns persisted regardless of age or performance status.

Cystic fibrosis mutation linked to pancreatic cancer

A registry study revealed that pancreatic cancer patients are more likely to have mutations in the cystic fibrosis transmembrane regulator (CFTR) gene than controls, reports an abstract presented at ASCO GI from the Mayo Clinic (abstract 187).

Mutations in the CFTR gene are well known to be associated with pancreatitis and pancreatic insufficiency. Furthermore patients with a clinical diagnosis of cystic fibrosis have been reported to show increased risk for young-onset pancreatic cancer.

In the study Robert McWilliams (Mayo Clinic, Rochester, Minnesota) and colleagues compared rates of 40 common CF disease associated mutations in 948 patients with pancreatic cancer and 13,340 controls, who had been taken from a prenatal testing database.

Results showed 5.3% of pancreatic cancer cases (50 out of 948) carried a detected CFTR mutation compared with 3.8% of controls (510 out of 13,340) ($P = 0.01$). Among those patients whose age of onset was under 60, the carrier frequency for a CFTR gene mutation was 6.8%.

Of the 50 pancreatic cancer patients with a mutation, 35 were found to have the Delta-F-508 mutation, which was also seen in 354 of the 510 controls with CFTR mutations.

For the 30 out of 50 pancreatic cancer patients who carried mutations who had smoked tobacco at some stage in their lives, the median age of onset for pancreatic cancer was 60.5 years. This was significantly lower than the median age of 65 for the 542 pancreatic cancer patients who had smoked at some stage in their lives, but were non carriers of the CFTR mutation ($P = 0.03$).

“Known CFTR mutation carriers should be counseled not to smoke, especially if they have other risk factor for pancreatic cancer such as diabetes, a family history of disease, and other factors,” said McWilliams.

Catumaxomab increases abdominal puncture time

Intraperitoneal therapy with the experimental monoclonal antibody catumaxomab resulted in significant improvements in overall survival and time to the next abdominal puncture, reported a UK phase II/III study in non-ovarian epithelial cancer patients with malignant ascites presented at ASCO GI (abstract 106).

Catumaxomab is a novel trifunctional antibody, being developed by Fresenius Biotech (Munich, Germany), which acts on two different antigen binding sites, the EpCAM (Epithelial Cell Adhesion Molecule) and the CD3 antigen expressed on T cells. Simultaneous binding appears to stimulate the immune system and increase tumour cell killing.

In the study a total of 129 non-ovarian epithelial cancer patients with recurrent malignant ascites were randomized to treatment with catumaxomab ($n = 85$) or to the control arm receiving paracentesis alone ($n = 44$). Catumaxomab was administered as a sequence of four intraperitoneal infusions of 10 mcg, 20 mcg, 50 mcg, and 150 mcg through 6-h infusions, following paracentesis on days 0, 3, 7, and 10.

Results show that the time from delivery of the drug to the need to perform a drainage procedure was 44 days for all gastric patients compared with 15 days for those who did not receive the monoclonal antibody ($P < 0.0001$). Furthermore, time between punctures was 115 days for patients who received catumaxomab compared with 14 days for patients who did not receive the drug ($P < 0.0001$). And time to progression was 110 days with catumaxomab, compared to 35 days for patients who did not receive the drug ($P < 0.0001$).

“The longer time to progression data suggest efficacy on the underlying tumor,” commented the principal investigator, Simon Parsons (Nottingham University, UK).

Data for catumaxomab in ovarian cancer were presented at ASCO last year.