2013 Gastrointestinal Cancers Symposium: meeting highlights

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The Gastrointestinal Cancers Symposium is an annual meeting geared toward physicians and researchers interested in the prevention, detection and treatment of gastrointestinal malignancies including medical, surgical and radiation oncologists, radiologists, gastroenterologists, pathologists and translational-oriented laboratory scientists.

The Gastrointestinal Cancers Symposium is a 3-day meeting covering a logical progression of topics from the upper to lower gastrointestinal (GI) tract – Thursday: cancers of the esophagus and stomach; Friday: cancers of the pancreas, small bowel and hepatobiliary tract; and Saturday: cancers of the colon and rectum. Each day begins with a session on prevention, screening and diagnosis, followed by a session focusing on translational research and selected oral abstracts and concluding with sessions on the multidisciplinary treatment of respective disease sites. The primary focus of this conference scene is to highlight notable data from cancers of the colon and rectum, as well as practice-changing data from other disease sites pertinent to GI oncology.

Colorectal cancer

Two trials in metastatic colorectal cancer (CRC) further clarified optimal chemotherapy (CT) regimens. The Italian TRIBE study randomized 508 previously untreated patients to 5-fluorouracil (5FU), leucovorin, oxaliplatin, irinotecan (FOLFOXIRI)/bevacizumab (bev) versus

5FU, leucovorin, irinotecan (FOLFIRI)/bev. The primary end point, progression-free survival (PFS), was improved from a median PFS of 9.5 months with FOLFIRI/bev to 11.9 months with FOLFOXIRI/bev ($p = 0.001$). Grade 3/4 GI toxicities were similar in both regimens with slightly higher rates of hematologic toxicities in the FOLFOXIRI/bev cohort [1]. A second multinational European trial evaluated the role of bev in addition to capecitabine (cap) in a relatively understudied population, the elderly. The AVEX trial randomized 280 patients ≥ 70 years old to cap versus cap/bev. Median age at enrollment was 76 and the primary end point was PFS. Patients receiving cap/bev had a significant increase in PFS of 9.1 months compared with 5.1 months with cap alone. A nonsignificant improvement in median overall survival (OS) was seen with cap/bev: 20.7 versus 16.8 months. As expected, rates of arterial and venous thromboembolism were nearly double with bev (3 and 8%, respectively). AVEX represents the first randomized trial evaluating the role of bev in elderly patients with metastatic CRC

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[2]. These trials indicate that the addition of new agents to standard CT regimens is associated with lower rates of disease progression with reasonable toxicity rates.

Unlike the robust data of the role of systemic therapy in the treatment of patients with metastatic CRC, the role of adjuvant CT in stage II colon cancer remains unclear. Common clinical practice is to recommend adjuvant CT for 'high-risk' stage II patients with one of the following characteristics: obstruction or perforation, T4 stage, fewer than 12 lymph nodes excised, involved surgical margins, lymphovascular invasion or perineural invasion. Data from the British Columbia Cancer Registry evaluated 1697 stage II patients treated between 1999–2008 (1236 high risk and 461 low risk). While most patients did not receive adjuvant CT, 29% of high-risk patients received adjuvant treatment. Individuals receiving adjuvant CT were younger with a better performance status. After adjusting for confounding variables, a statistically significant survival advantage was seen in patients with high-risk features receiving adjuvant CT: 5-year OS: 75% with adjuvant CT compared with 68% with no adjuvant CT. However, relapse-free survival and disease-specific survival benefits were seen in T4 patients suggesting a limited role for CT in 'high-risk' patients and possible trend towards harm in a low-risk group receiving CT [3]. Retrospective analyses such as these are limited by patient selection.

For patients with stage II–III rectal cancer the standard of care throughout most of the USA and parts of Europe is neoadjuvant, long-course chemoradiation. A number of studies have indicated superior outcomes in patients who achieve a pathologic complete response (pCR), with some studies suggesting that patients achieving a complete clinical response may, with close surveillance, forego surgical resection [4,5]. Efforts to optimize neoadjuvant regimens to obtain higher pCR rates have been the focus of ongoing study as reflected in a number of abstracts from this year's meeting. A Phase II study from Brown University (RI, USA) reported on the feasibility of delivering all planned CT in the neoadjuvant setting and its impact on pCR

and complete resection (R0). Of a planned 39 patients with locally advanced rectal cancer, 36 received modified FOLFOX6 every 2 weeks for eight cycles, followed by chemoradiation (CRT) with 5-FU-based CT and surgical resection within 4–8 weeks. A total of 26 patients completed all planned preoperative therapy with 21 patients undergoing surgical resection. R0 resections were achieved in 100% of patients with six (29%) demonstrating pCR [6]. A second Phase II study reported on 37 of a planned 55 patients with locally advanced rectal cancer, delivering a neoadjuvant regimen of oxaliplatin, capecitabine and celecoxib with concurrent radiotherapy (RT). A total of 21 patients underwent surgery with complete pathologic evaluation. Of these, seven (33%) had a pCR [7]. Phase III data with the addition of oxaliplatin to 5FU-based CRT have shown no significant improvement in pCR or clinical outcomes with higher rates of toxicities; the effect of celecoxib and other agents concurrent with radiation may warrant further investigation [8–10].

As emerging data has shown short-term equivalence of neoadjuvant, long-course CRT and short-course RT in terms of local control in rectal cancer patients, some neoadjuvant studies are utilizing a short-course approach for RT delivery [11,12]. A Phase II study of 80 patients with cT3–T4 rectal cancer from Washington University, USA initiated neoadjuvant treatment with short-course RT (5 Gy × five fractions) followed by four cycles of mFOLFOX6. Of 76 evaluable patients, 21 (28%) achieved a pCR, with only 9% experiencing grade 3 GI toxicity during neoadjuvant therapy [13].

Noncolorectal cancer

Clinical research in GI malignancies has focused on the integration of targeted agents into therapy, particularly EGF receptor (EGFR) and VEGF inhibitors, which are involved in tumorigenesis and metastasis development. An important lesson reiterated in this year's meeting is that an agent that has been shown to be efficacious in the metastatic setting does not necessarily translate to improved outcomes in patients with localized disease. Data in the metastatic setting show improved outcomes

with the addition of trastuzumab (a monoclonal antibody against human HER2/EGFR2) to standard CT for patients with advanced gastric or gastroesophageal junction cancers exhibiting HER2 overexpression [14]. In head and neck squamous cancers, the addition of cetuximab to RT resulted in a significant improvement in OS [15]. Nearly 80% of esophageal adenocarcinomas and squamous cell carcinomas overexpress EGFR and hence inhibition of this pathway may represent an important therapeutic target [16].

A multicenter Phase II/III trial from the UK randomized 258 patients with esophageal cancer with plans for definitive CRT with cisplatin/capecitabine to treatment with or without cetuximab. The Phase II primary end point, 24-week failure-free survival in the cetuximab arm, was not met and the trial was closed on the basis of futility. Patients receiving cetuximab experienced higher rates of nonhematologic toxicities and lower rates of standard treatment completion. A significant detriment to median OS was seen with the addition of cetuximab (22 vs 25 months) [17]. Results from this study prompted the suspension of recruitment to RTOG 0436, a randomized study evaluating the addition of cetuximab to paclitaxel, cisplatin and RT in patients with esophageal cancer treated without surgery. In pancreatic cancer, an interim analysis of an ongoing Phase III Japanese trial comparing adjuvant S1 versus gemcitabine in resected pancreatic cancer patients was reported. S1 is an oral fluoropyrimidine that combines tegafur, gimeracil and oteracil, and has previously been shown to enhance survival in Japanese patients undergoing gastric cancer resection [18,19]. In the pancreatic study, a preplanned interim analysis after the first 205 deaths (in 385 patients) showed that 70% of S1 patients were alive at 2 years follow-up compared with 51% receiving gemcitabine, with corresponding 2-year disease-free progression rates of 49 versus 29%, respectively [20]. In patients with locally advanced pancreatic cancer, a randomized Phase II study of induction CT followed by gemcitabine versus capecitabine-based chemoradiation was reported. Patients received three cycles

of gemcitabine/capecitabine CT initially and those with stable/responding disease, tumor diameter ≤ 6 cm and favorable performance status received a further cycle of the same CT and were then randomized to either capecitabine-based CRT versus gemcitabine-based CRT. Primary study end point was 9-month PFS. Grade 3/4 hematologic and nonhematological toxicity was higher in the gemcitabine arm, with a 9-month PFS (63 vs 51%) and OS (15.2 vs 13.4 months) improved in the capecitabine-containing arm [21]. In patients with metastatic pancreatic cancer, a randomized Phase III study of weekly nab-paclitaxel plus gemcitabine versus gemcitabine alone (the MPACT study) was reported. Nab-paclitaxel is an albumin-bound drug that provides tumor-selective localization via transcytosis across the endothelium, potential tumor uptake via macropinocytosis and improved pharmacokinetics versus unbound paclitaxel, while also demonstrating increased tumoral gemcitabine levels *in vitro*. In this study of 861 patients OS (8.5 vs 6.7 months median), PFS (5.5 vs 3.7 months median) and time to treatment failure (5.1 vs 3.6 months median) were significantly improved in the nab-paclitaxel-containing arm [22].

Conclusion

Few conferences address prevention, diagnosis, treatment and management of patients with GI malignancies in a true multidisciplinary forum. Data presented at this year's conference will continue to help shape and guide contemporary treatment approaches as well as facilitate future breakthroughs in gastrointestinal cancers.

Financial & competing interests disclosure

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