

International Society of Gastrointestinal Oncology
2009 Gastrointestinal Oncology Conference
October 1–3, 2009
ABSTRACTS

Gastric Cancer

abstr 0946

Advanced Gastric Cancer: An Update

Al B. Benson III, MD, FACP

Professor of Medicine, Associate Director for Clinical Investigations, Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Feinberg School of Medicine, Chicago, IL

Worldwide, gastric cancer continues as a significant healthcare issue with an unacceptably high mortality rate. Although it is clear that combination chemotherapy for advanced gastric/esophageal gastric cancer is superior to best supportive care and monotherapy, the median survival over the past two decades persists at less than 10 months. Multiple combination regimens have been evaluated in the phase III setting, producing response rates ranging between 9% and 45%. There is still debate as to whether doublet vs. triplet chemotherapy combinations represent the most appropriate platform from which to build other regimens, including those with biologic therapy.

Two published clinical trials have significantly influenced clinical practice. A randomized trial including 545 advanced gastric cancer patients compared first-line treatment with DCF (docetaxel, cisplatin, 5-FU) vs. the cisplatin/5-FU regimen. The cisplatin/5-FU combination has, over time, become a standard comparator regimen and has been supported by the FDA. Although the trial showed a significant survival advantage favoring DCF, there has been concern about toxicity, particularly the risk of increased diarrhea, neutropenia, and neutropenic fever. The REAL2 trial was a 2x2 randomized, first-line advanced gastric cancer study that compared two different platinum compounds and two different fluoropyrimidines in combination therapy. The regimens consisted of ECF (epirubicin, cisplatin, and infusional 5-FU), ECX (epirubicin, cisplatin, and capecitabine), EOF (epirubicin, oxaliplatin, and infusional 5-FU) and EOX (epirubicin, oxaliplatin, and capecitabine). The authors concluded that the oxaliplatin combinations appeared to be safer than those with cisplatin and that oxaliplatin was not inferior to cisplatin, nor was capecitabine inferior to infusional 5-FU. Furthermore, EOX appeared to have improved efficacy compared to the reference regimen (ECF).

The National Comprehensive Cancer Network (NCCN) has encompassed a listing of potential combination regimens for metastatic or locally advanced cancer in the Clinical Practice Guidelines. The NCCN cites category 1 level of evidence in support of DCF and ECF, with category 2B evidence and

International Society of Gastrointestinal Oncology
2009 Gastrointestinal Oncology Conference
October 1–3, 2009
ABSTRACTS

Gastric Cancer

consensus for irinotecan plus cisplatin, oxaliplatin plus a fluoropyrimidine, DCF modifications, irinotecan plus fluoropyrimidine, and paclitaxel-based regimens.

A recently completed ECOG/CALGB collaborative, randomized phase II trial (E1206/C80403) is of interest since it integrates the monoclonal antibody cetuximab as a component of three different platform regimens: ECF, irinotecan and cisplatin, and FOLFOX (5-FU, oxaliplatin, and leucovorin). A significant challenge for future trial design will continue to address optimal chemotherapy platforms and how to best choose among a host of different biologic agents to potentially improve median survival. Identifying tumor-specific molecular/genetic characteristics that will help inform the choice of biologic agents is a significant obstacle.

A trial that generated considerable interest during the American Society of Clinical Oncology (ASCO) 2009 meeting evaluated the addition of trastuzumab to standard first-line chemotherapy for patients with human epidermal growth factor receptor (HER2)-positive advanced gastric cancer (ToGA trial). The trial screened 3,807 patients to identify the 22.1% who were HER2-positive and were subsequently randomized to receive 5-FU or capecitabine plus cisplatin (n=290) vs. 5-FU or capecitabine plus cisplatin plus trastuzumab (n=294). The trial stratified patients on the basis of gastric vs. GE cancers, measurable vs. nonmeasurable disease, ECOG performance status, capecitabine vs. 5-FU, and advanced vs. metastatic disease. Assessment was by central evaluation and included immunohistochemistry (IHC) 3+ and/or FISH+. Patients who received trastuzumab had a significant improvement in overall survival, which was the primary study end point, as well as a significant improvement in progression-free survival. Toxicity was considered acceptable, including incidence of cardiac toxicity.

During ASCO 2009, there was also an update of the FLAGS study, a randomized phase III trial comparing cisplatin/S1 (CS) with cisplatin/5-FU (CF) as first-line therapy in patients with advanced gastric cancer. This follow-up analysis confirmed the initial findings, demonstrating that the CS regimen was not inferior to CF and appeared to be safer. An unplanned subset analysis was of interest, because it suggested a significant increase in the diffuse type of gastric cancer since 1973 and a significant decrease in the intestinal type of gastric cancer. Results of the unplanned analysis also suggested that the

International Society of Gastrointestinal Oncology
2009 Gastrointestinal Oncology Conference
October 1–3, 2009
ABSTRACTS

Gastric Cancer

S1/cisplatin combination may be more effective in patients with the diffuse type of pathology, and this will require further investigation in prospective studies.

Finally, another trial updated during ASCO was the randomized phase III study of single-agent 5-FU vs. the combination of irinotecan and cisplatin vs. single-agent S1 in advanced gastric cancer (JCOG9912). The initial analysis demonstrated the superiority of irinotecan with cisplatin compared to continuous-infusion 5-FU and the non-inferiority of S1 compared to infusional 5-FU. This updated analysis showed that overall survival and hazard ratios were identical to those in the previous reports. In addition, multivariate analysis showed that the number of metastatic sites, performance status, and presence of target lesion were associated with shorter survival.