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Advanced Gastric Cancer: An Update and Future Directions

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Although of relatively low incidence in the United States, gastric cancer is a common disease worldwide with a high mortality rate because of the late-stage at diagnosis in many cases and high relapse rates. Gastric cancer is clearly a complex disease with many clinical, pathologic, and molecular/genetic features. The expanding list of potential molecular markers for gastric cancer provides the opportunity to better understand the biology of the disease and to develop new treatment strategies. Several single agents have been evaluated, including platinum compounds, taxanes, anthracyclines, fluoropyrimidines and, more recently, targeted therapies have entered into the clinical trials arena. Response rates for single-agent therapy have ranged from less than 5% to as high as 45%.

The majority of patients receive combination chemotherapy regimens, which appear to increase response rates as demonstrated in a number of phase II trials. Response advantage for combination chemotherapy has also been demonstrated in phase III trials, although the overall response rates tend to be lower than in phase II observations. The benefits of combination therapy have been suggested in comparisons to previous data with best supportive care, with more than a doubling in survivorship achieved with therapy vs. best supportive care. There is also a suggestion that adding a third drug to treatment may improve the overall response rate. The V325 phase III advanced gastric cancer trial comparing docetaxel, cisplatin, and 5-FU (DCF) vs. cisplatin and 5-FU (CF) has been reported in the *Journal of Clinical Oncology*. The trial demonstrated an overall survival advantage for patients receiving the DCF regimen ($P=.02$; hazard ratio, 1.293; risk reduction, 22.7%). There were important toxicity concerns with DCF, including a

high rate of neutropenia and neutropenic fever; however, an assessment of quality of life appeared to favor the DCF regimen. Randomized trials have also compared irinotecan and 5-FU vs. cisplatin and 5-FU, showing comparable response rate, time to progression, and overall survival. The REAL-2 trial presented at the 2006 American Society of Clinical Oncology annual meeting incorporated a 2×2 randomization evaluating epirubicin and cisplatin with either infusional 5-FU or capecitabine, and epirubicin and oxaliplatin with either infusional 5-FU or capecitabine. The overall survival was superior for the EOX (epirubicin, oxaliplatin, capecitabine) regimen ($P = .02$). In addition, oxaliplatin-containing triplets appeared to have a favorable safety profile compared with the cisplatin-containing triplets.

Additional randomized data are available for the oral fluoropyrimidine, S-1. S-1 is an oral formulation of tegafur, CDHP (5-chloro-2, 4-dihydroxypyridine), and potassium oxonate. In the randomized trial comparing 5-FU vs. irinotecan plus cisplatin vs. S-1 conducted by the Japan Clinical Oncology Group, S-1 was associated with a favorable safety profile, response rate, and time to treatment failure, with longer survival compared with 5-FU. The Japanese SPIRITS trial was a phase III comparison of S-1 vs. S-1 plus cisplatin. Results showed favorable 1- and 2-year survivals and a progression-free survival advantage for S-1 and cisplatin.

Cooperative group strategies are evaluating the role of chemotherapy combinations including cisplatin and docetaxel with biologic agents. In addition, there is interest in developing oxaliplatin-based combinations. The evaluation of molecular alterations is also an important component of research endeavors.