Meaningful improvement in the chemotherapy of gastrointestinal malignancies continues to be an elusive and challenging target in the 1990s. However, although real and tangible advances have been scarce, particularly in the setting of widespread metastatic disease, whatever its origin, there are indications of notable progress in a few selected situations.

Beginning with esophageal cancer of both the adenocarcinoma and squamous variety, it would appear that combined modality therapy is here to stay. Most cancer programs now advocate chemotherapy, usually cisplatin and 5-fluorouracil together with radiation therapy, prior to definitive esophagectomy for localized disease. An exciting advance is the discovery of the activity of paclitaxel in this setting, and it is currently being tested in combination with both cisplatin and carboplatin as well as 5-fluorouracil early indications of success. In this regard, an ongoing protocol at the University of Florida using two to four cycles of carboplatin and paclitaxel followed by continuous infusion 5-fluorouracil and radiation therapy prior to surgery continues to accrue patients and, together with other phase two studies of a similar nature, will help to define the optimal use of paclitaxel in this disease. If its initial promise is confirmed, it is likely that this agent will become an integral component of the new standard of care.

In locally advanced and metastatic gastric cancer, the search for effective combination chemotherapy continues. Every year it seems that a new champion is declared, and 1997 was no different with the pronouncement that first ECF (epirubicin, cisplatin, and continuous infusion 5-fluorouracil) and then PELF (cisplatin, epirubicin, leucovorin, and 5-fluorouracil) were the new “state-of-the-art” programs of choice. With neither combination able to achieve a median survival in excess of 11 months, it remains to be seen whether the toxicity and cost of these regimens are truly justified in terminally ill patients who want the best possible quality of life in their remaining few months. There appears to be no substantial advance in this regard over the older protocols such as ELP (etoposide, leucovorin, and 5-fluorouracil) and EAP (etoposide, doxorubicin, and cisplatin).

The situation is somewhat brighter in colorectal cancer. Once again, the application of combined modality therapy together with improved chemotherapy agents and improved knowledge of their use means that more patients with previously untreatable or terminal illness will now have a realistic chance of either obtaining a remission or prolonging their lives. The optimal method of administering 5-fluorouracil continues to evolve, and, unlike gastric cancer, there appears to be progress with each new iteration.

Adjuvant chemotherapy of Astler-Coller stages B2 and C disease has been widely adopted in the United States, if not necessarily elsewhere, and it appears that 12 months of 5-fluorouracil and levamisole may ultimately give way to six months of 5-fluorouracil and leucovorin as the preferred regimen in those who can tolerate the somewhat increased intensity. In the setting of metastatic or locally advanced disease, application of chronotherapy and/or the addition of oxaliplatin has added a further dimension to the advances already achieved by the addition of either high- or low-dose calcium leucovorin to most regimens.

Our current program of 14-day continuous chronomodulated infusion of 5-fluorouracil and leucovorin, which is a concurrent effort with the University of Toronto, continues to rapidly accrue patients. Updated results indicate a 45% overall response rate in previously untreated patients, including a 15% complete response rate. A further 35% of patients maintained stable disease. Trials from France, which have included oxaliplatin in a five-day continuous circadian infusion, have elicited a similar response rate (53%). In all of these trials, the gratifyingly low toxicity has meant that the quality of life of these patients has been relatively unaffected.

A new option now being tested in large cooperative group phase II trials is the combination of oral 5-fluorouracil and oral ethylnyluracil, a uracil analogue that irreversibly inactivates DPD (dihydropyrimidine dehydrogenase), the principal enzyme responsible for the degradation of 5-fluorouracil. This action allows much more consistent absorption of 5-fluorouracil from the gut, as a good deal of DPD is found there, and also leads to significant prolongation of the half-life of 5-fluorouracil from approximately 13 minutes to 3-1/2 hours. When given daily for extended periods, it is hoped that the results will mimic those of prolonged infusions of 5-fluorouracil.

Finally, the consistent 15% response rate achieved with the use of CPT 11 in 5-fluorouracil refractory patients has confirmed this agent as the standard of care in this setting. Most oncologists have now learned how to administer it safely and how to manage the potential complications, despite its relatively narrow therapeutic index. Trials to determine its possible role in combination therapy of de novo disease are currently underway.

Gemcitabine has been rapidly embraced by most physicians as the therapy of choice in inoperable patients with pancreatic cancer. For the first time, it appears that there is finally a chemotherapy agent that impacts favorably on the quality, and perhaps even the quantity, of life of these seriously ill individuals. In addition, gemcitabine is capable of radiosensitizing a tumor, and this beneficial effect is under active investigation. In truly localized disease, a combination of 5-fluorouracil and radiation therapy followed by gemcitabine is showing considerable promise in early testing.

In cases of rectal cancer, preoperative and/or postoperative chemotherapy as part of a multimodality approach has significantly impacted the quality of life and also survival of patients so treated. Continuous infusion of 5-fluorouracil (chronomodulated at the University of Florida) has become an integral part of these programs owing to the improved results so obtained, and this finding once again confirms the superiority of this method of administration in most settings. The dual goals of resection of tumor and rectal sparing are now achievable in a large percentage of cases, despite an often grim outlook at first evaluation. Despite these advances in the United States, colleagues in Europe steadfastly believe that proper surgical technique can achieve similar results, and they have not as yet embraced this approach with enthusiasm.

The therapy of anal cancer, one of the more successfully treated sites in the gastrointestinal tract, has not seen any dramatic innovations in the last few years, but there is one potentially important evolution in the wings. It appears that cisplatin may possibly be used instead of mitomycin-C in combination with 5-fluorouracil and radiation therapy for the definitive treatment of this condition. Although final data are not yet available from the definitive Eastern Cooperative Oncology Group trial, those institutions that have actively pursued this line of investigation (including the University of Florida) and confidently predict that the result will be favorable with respect to the use of cisplatin.

Finally, the use of octreotide in carcinoid syndrome and other active neuroendocrine tumors has enabled investigators to explore newer techniques of treatment such as embolization without fear of devastating consequences for the patient. In selected situations, this can mean the difference between asymptomatic remission and lifelong threatening inanition. Most large centers now routinely perform embolization in these diseases with relative impunity. Unfortunately, diseases such as hepatocellular carcinoma and biliary tract malignancies remain difficult, if not impossible, to treat with any degree of success, and any progress in these areas will be welcomed. It is hoped that some of the newer classes of drugs, such as angiogenesis inhibitors, will perhaps have some activity in these areas.
References


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