ABSTRACT

In the preceding articles, issues pertaining to staging and treatment of advanced colorectal and gastroesophageal cancers were addressed. Here these issues are integrated, summarized, and future directions projected. Although the prognosis for advanced colorectal or gastroesophageal disease is still poor, the past decade has seen a tremendous improvement. In addition to the newer cytotoxic agents, such as irinotecan and oxaliplatin, biological agents targeting vascular endothelial growth factor and epidermal growth factor signaling have begun to be tested in clinical trials in combination with the older drugs. Molecular studies are continuing to identify new targets and new agents that may prove to be efficacious. Imaging techniques are allowing better assessment of early disease and disease after surgery. Additionally, surgical techniques have improved such that we are now seeing more patients qualifying for resection than ever before. Indeed, it is now not uncommon for chemotherapy to render a formerly unresectable patient resectable. Thus, with new drugs available and new ways to use them, we are only at the beginning of the process of defining optimal treatment regimens. The fluoropyrimidine drugs have been reformulated, and it is predicted that the decrease in toxicity resulting from these reformulations will add months to overall survival. Tools for screening heterogeneous patient populations are being validated, allowing clinicians to assess who is in need of resection alone and who is in need of resection plus adjuvant therapy. New paradigms are leading to new primary outcomes in clinical trials that will speed the process of evaluation and increase patient quality of life. We are seeing a trend towards a unique treatment plan for each patient, and this process will only increase in the foreseeable future.


SUMMARY AND FUTURE DIRECTIONS FOR INVESTIGATIONS IN COLON AND GASTROESOPHAGEAL CANCERS

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IMPROVEMENTS IN CHEMOTHERAPEUTIC DRUGS AND DRUG FORMULATIONS

When one considers colorectal cancer (CRC) and other gastrointestinal (GI) malignancies before 1998, there was 1 available drug: the fluoropyrimidine, 5-fluorouracil (5-FU). Then, in 1998 irinotecan was approved by the US Food and Drug Administration. Subsequently, we have seen several new drugs become available, including oxaliplatin, cetuximab, panitumumab. Additionally, old drugs have found new life in new formulations. 5-FU was originally augmented with leucovorin administered intravenously as a bolus. Bolus administration is being replaced by continuous infusion, which has worked to decrease toxic side effects. Capecitabine is an orally administered fluoropyrimidine carbamate that has the same mechanism of action as 5-FU. Oral administration allows a slow and continual introduction of 5-FU in the outpatient setting. Finally, the newest form of fluoropyrimidine formulation, S-1, consists of tegafur
(a prodrug that is converted to 5-FU by cytochrome P450 2A6) in combination with several enzyme inhibitors, which modify the way in which 5-FU is metabolized, further decreasing toxicity. This increase in the number of available drugs has been mirrored by an increase in overall survival. Importantly, the work of Axel Grothey, MD, has shown us that although it is important to expose patients to the right drug, patients exposed to several drugs during the course of their treatment will have an increased overall survival. His meta-analysis of several independent studies demonstrated that this result was independent of which treatment was first-line and which functioned as a second-line therapy.

One can map the increase in overall survival in metastatic CRC as a function of formulations and combinations of chemotherapeutic agents. On best supportive care the overall survival averages 4 to 6 months. This is increased to 11.3 months with bolus 5-FU/leucovorin. Moving from bolus administration of 5-FU to continuous infusion decreased toxicities and increased overall survival to 12.1 months. When 5-FU infusion was replaced by the oral formulation, capecitabine, overall survival was further increased to 13.2 months. Combining the camptothecin, irinotecan, with bolus 5-FU/leucovorin further increased overall survival to 14.8 months whereas combining irinotecan with infusional 5-FU/leucovorin increased overall survival to 17.4 months. In another study the combination of bolus 5-FU/leucovorin plus either irinotecan or the third-generation platinum compound, oxaliplatin resulted in a similar overall survival of 17.6 months. Oxaliplatin, when combined with infusional 5-FU/leucovorin, resulted in an overall survival of 19.5 months. With the advent of the targeted biological agents even more combinations were tried. Of note, the combination of irinotecan plus bolus 5-FU with the addition of the anti-vascular endothelial growth factor (VEGF) monoclonal antibody, bevacizumab, resulted in an overall survival of 20.3 months. In a separate study, this was followed by treatment with oxaliplatin resulting in an overall survival of 25.1 months. Thus there has been a steady increase in overall survival over the past 5 years as new chemotherapeutic combinations continue to be explored.

**NEW TREATMENT PARADIGMS**

To date, the biological agents have been reserved for metastatic CRC. However, a trend that we are now seeing is for the use of these agents in the adjuvant setting. For example, in John L. Marshall, MD's article, the Eastern Cooperative Oncology Group 5202 trial was described, in which patients with stage II CRC are being divided into high-risk and low-risk groups on the basis of chromosome 18q loss of heterozygosity and microsatellite stability. Whereas the low-risk group will simply be monitored, the high-risk group will receive modified FOLFOX4 (5-FU, leucovorin, and oxaliplatin) or FOLFOX4 plus bevacizumab. Additionally, the National Surgical Adjuvant Breast and Bowel Project C-08 and AVANT trials are looking at bevacizumab in the adjuvant setting. In the intergroup trial N1047 patients are receiving modified FOLFOX6 or modified FOLFOX6 plus cetuximab, again in the adjuvant setting. Gastroesophageal cancers also are being attacked with new agents. Jaffer A. Ajani, MD, has described the use of docetaxel in a large phase III trial and additionally has described the ongoing FLAGS trial exploring the use of S-1.

With the advent of new therapies and new therapeutic combinations, several important questions were raised in the article by Daniel G. Haller, MD. How do these drugs fit in? Should we give these drugs to everyone? Do we limit therapy or do we continue it indefinitely? How should we choose? Is the intent curative or palliative? What should we do about the symptoms that patients experience? As we increase the number of drugs included in the regimen for patients, we also increase the potential side effects and toxicities. Should we give patients receiving chemotherapy holidays to decrease the possibility of these side effects and, if so, what therapies are admissible during those holidays? We are beginning to find answers to these questions but it is slow work. Addressing these questions has led to new paradigms in the treatment of colorectal and gastric cancers. Endpoints for clinical trials are extending beyond simple overall survival. As described by Dr Ajani, quality-of-life (QOL) measures in some contexts are very important. However, as he also has shown, it seems that one cannot easily dissociate efficacy and QOL. Generally, if there is no change in efficacy with a new regimen, there is also no change in QOL. Additionally, by using surrogate markers as clinical endpoints it will become possible to assess the efficacy of new drugs at early stages in the treatment process, allowing patients to move on to more effective therapies. For example, expansion of a tumor beyond 2 mm³ requires the presence of a specialized vascular network, which can supply the tumor with nutri-
Imaging techniques (to be described next) have been developed to assess the vasculature in a noninvasive fashion. Thus there is the possibility of assessing the efficacy of antiangiogenic therapies at early time points in the treatment process.

**Molecular Markers**

What does the future hold for patients suffering from this disease? The heterogeneity in the GI cancer population has led to a heterogeneity of response to chemotherapy. Some patients will be cured by resection whereas others will require resection plus adjuvant chemotherapy. Although some patients with metastatic CRC respond well to irinotecan plus 5-FU/leucovorin, others respond to oxaliplatin plus 5-FU/leucovorin. This ultimately is caused by the interplay of the genetics of the patient and the mutagenesis of the cancer. We are just beginning to identify the critical genes that play a role in this process. These genes hopefully will serve as predictive markers for the patient’s response to a particular regimen. Hereditary nonpolyposis colorectal cancer (HNPCC) accounts for 3% to 4% of CRC and involves defects in the mismatch repair mechanism for DNA. Microsatellite DNA instability is easily assessed from tumor specimens, allowing for an inexpensive and robust method of identifying the condition after the tumor is resected or biopsied. However, methods for predicting the likelihood of HNPCC in healthy family members are still being developed. The difficulty lies in the issue that several different genes could be mutated, leading to this condition. Screening the family of mismatch repair genes for mutations is labor intensive and still not completely accurate. Several groups have recently developed multivariate HNPCC predictive models on the basis of personal and family history of cancers.

In addition to improving the ability to predict the risk of cancer in the healthy population, intense research is being performed looking for genetic markers that will help characterize an established cancer as low risk (needing resection only) or high risk (needing resection plus adjuvant chemotherapy). Additionally, markers are being sought that will predict the efficacy of the various treatment regimens described above. Dr Marshall has described work exploring the predictive capabilities of mutations in p53, k-ras, DCC, and thymidylate synthase genes. Of these, only DCC mutations have been found to have robust predictive value. As DCC is located on chromosome 18q, loss of this chromosome (which is easily measured) is currently being used effectively as a means to predict risk; however, the search is far from over. As an example of some of the newer paradigms being explored, one group has recently examined the genetics of the body’s response to the tumor by focusing on genes expressed uniquely by the immune cells that have infiltrated the tumor. By performing genomic and in situ hybridization analysis on more than 400 tumor specimens from patients with CRC and looking for correlations between gene expression and survival, they found that genes associated with the presence of the Th1 T cell subtype correlated inversely with tumor recurrence survival. This and similar findings are likely to greatly improve our abilities to predict the behavior of patients with stage II CRC.

DNA methylation is an important epigenetic phenomenon that plays a central role in colorectal and gastric cancers. Methylation of promoter regions can shut down the expression of genes involved in tumor suppression. This has been proposed as a therapeutic target in addition to an indicator of risk and possibly a means of early detection. One interesting gene that has emerged as a risk prediction assessment tool is insulin-like growth factor (IGF)-2. Normally, 1 copy of the IGF-2 gene is silenced through a methylation process called imprinting. Biallelic expression of IGF-2 represents a loss of imprinting (LOI), which is caused by hypermethylation of a DNA region known as H19. A study of 172 colonoscopy subjects that looked at IGF-2 LOI in blood samples found an odds ratio of 21.7 for patients with CRC and 5.15 for patients with a family history of CRC. Unfortunately, IGF-2 LOI is also associated with lymphocyte activation, creating a high likelihood of false positives generated by this assessment tool. In any event, studies of DNA methylation will most likely give us important new tools in the near future.

**New Imaging Technologies**

Another important area where advancement is being made is imaging. This will play a role in the early detection of tumors and the monitoring of success after resection. Recent examples of advances in this area include the use of dynamic contrast enhanced magnetic imaging (DCE-MRI) and positron emission tomography (PET) techniques to image tumor vascularization and the effect of antiangiogenic therapies. A
study examined 26 patients with CRC who were undergoing a phase I dose escalation trial using 1-(4-chloroanilino)-4-(4-pyridylmethyl) phthalazine succinate (PTK787/ZK 222584), the protein tyrosine kinase inhibitor that blocks VEGF signaling. The authors were able to successfully correlate dye transfer as inversely proportional to the dose of PTK787/ZK 222584, in addition to the patient response to therapy. PET has traditionally been best used in drug distribution studies. In the future, PET will be combined with DCE-MRI to allow co-registration methodologies to be developed. In this fashion, DCE-MRI images can be merged with PET-generated data, such as tumor metabolism, tumor DNA synthesis, and apoptosis of tumor cells. These comparisons will make possible the interpretation of how drug distribution may affect vascularization and visa versa.

By taking a multidisciplinary approach, clinicians will be better able to treat the patient. Surgery, radiation therapy, and chemotherapy will all have a place in this system and molecular markers will be established to identify which patient groups are best served by which treatment modalities. Therapies that were once only used for advanced metastatic cancer will be used in the adjuvant setting, and improved surgical techniques will allow a greater number of cases to be resected after chemotherapy.

CONCLUSIONS

The discovery of new drugs and new formulations has complicated the treatment of colorectal and gastric cancers in a positive manner. We can now begin to tailor treatments of the cancer to the patient. The future of the field will be dominated with the introduction of even newer drugs raised against old and new molecular targets. It is quite conceivable that regimens made up of many drugs may become common. We will see many new clinical trials over the next few years assessing appropriate combinations of these drugs to create more efficacious regimens. Molecular markers will continue to be identified to establish risk and allow early detection. Imaging techniques will add to our ability to detect early disease and monitor the treatment of advanced disease. Cancers will be more accurately staged and patient responses to therapies more accurately predicted. Supportive care will improve to render toxicities less problematic. QOL measures will become more commonplace, allowing patients to give input into their treatments and to give caregivers a better sense of how to help their patients live with their disease. More and more we will see these patients move beyond simply living with the disease to achieving a cure.

REFERENCES


