

Advances in Systemic Therapy for Colorectal Cancer

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Summary

Colon cancer is an immensely complex disease whose treatment is changing rapidly. The treatment advances in the past five years have been tremendous. Significant effort is currently ongoing to determine how to optimally manage each patient. There are frequently updated clinical guidelines to help guide appropriate treatment decisions, but flexibility must be maintained in order to optimize treatment for the individual.

Key Points

- Stage I to III colon cancer is curable.
- At this time Stage IV disease is not curable.
- Exposing a patient to the three effective chemotherapy agents (5-Fluorouracil/Leucovorin/Oxaliplatin) appears optimal for managing advanced disease.
- New non-chemotherapy biologic agents also are used to improve survival.

COLORECTAL CANCER IS THE THIRD most frequently diagnosed cancer in men and women in the United States. Approximately 100,000 new cases of colon cancer occur each year and 50,000 people will die from colon and rectal cancer.¹ Despite these statistics, mortality from colon cancer has decreased during the past 30 years, possibly because of earlier diagnosis through screening and better treatment modalities.¹

Exhibit 1 outlines the stages of colon cancer.² When the disease is caught early (Stages I – III) it is curable. A critical piece of information learned about colorectal cancer is that some patients with metastatic disease can be cured. In the past, many patients with Stage IV disease were considered incurable. One of the goals in colon cancer treatment is to continue making advances in treating the most advanced stages.

Until the late 1990s, the only chemotherapy agent available for treating colon cancer was fluorouracil (5-FU), which is always given with leucovorin to minimize adverse effects. Several new chemotherapy agents have been approved in recent years [irinotecan (Camptosar[®]), capecitabine (Xeloda[®]), and oxaliplatin (Eloxatin[®])]. New agents have come so quickly that oncologists have had difficulty knowing exactly how to deploy them in a patient.

Capecitabine (Xeloda[®]) is one of the advances in the treatment of colon cancer. It is an oral pro-drug of 5-FU. The advantage of this oral agent is its ability to get rid of the pumps and the infusion devices for 5-FU. With this agent, finding the right dose remains a challenge. Much of the data on capecitabine comes from European studies, where the drug was first developed. In the United States, patients receiving the doses used in the European studies have much greater toxicity. Interestingly, this may be because many food products in the U.S. are supplemented with folate, which is in contrast to many European countries with limited folate supplementation. It is thought that the high folate content of the diet in the United States contributes to excessive toxicity of this oral drug.

Capecitabine also has many interactions with other medications. However, capecitabine is a very promising drug for simplifying therapy.

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in oncology detail the recommended therapies for colon cancer. For example, a portion of one of the algorithms is given in Exhibit 2.¹ These guidelines have very complex algorithms with many options for every patient at each step of the way. Depending on the details of their case, there are many different

Exhibit 1: Staging of Colorectal Cancer

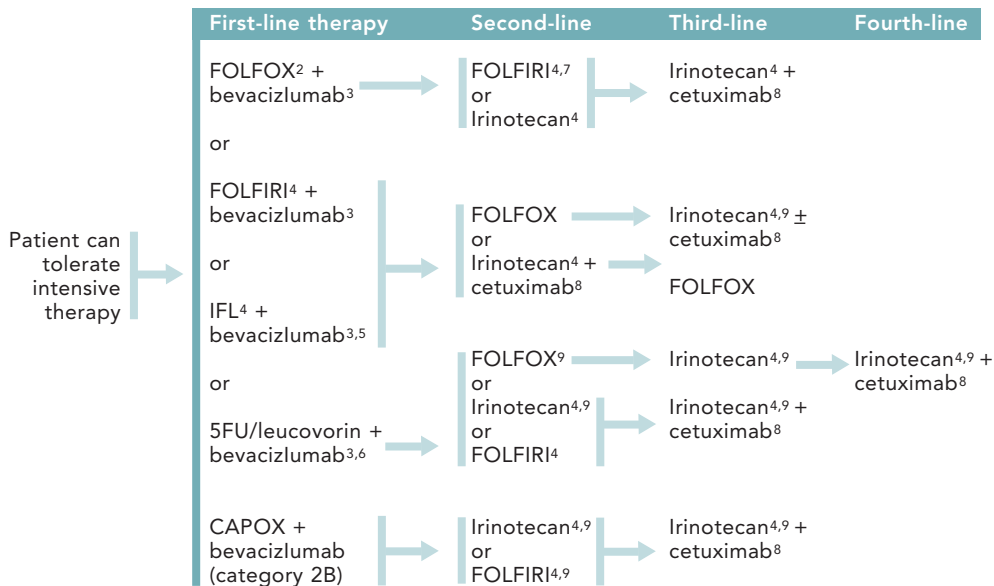
Stage	A	B ₁	B ₂	C ₁	C ₂	D
Extent of tumor	No deeper than submucosa	Not through bowel wall	Through bowel wall	Not through bowel wall: lymph node metastases	Through bowel wall: lymph node metastases	Distant metastases
5-year survival	> 90%	80–85%	70–75%	50–65%	25–45%	< 5%

The diagram shows a cross-section of the bowel wall layers: Mucosa, Muscularis mucosa, Submucosa, Muscularis propria, Serosa, Fat, and Lymph nodes. Stage A shows tumor confined to the mucosa. Stage B₁ shows tumor through the muscularis mucosa but not the submucosa. Stage B₂ shows tumor through the submucosa but not the muscularis propria. Stage C₁ shows tumor through the muscularis propria but not the serosa, with lymph node metastases. Stage C₂ shows tumor through the serosa with lymph node metastases. Stage D shows distant metastases.

Adapted from Skarin. *Slide Atlas of Diagnostic Oncology*. Gower Medical Publishing; 1997: Fig 5.98.

Exhibit 2: Colon Cancer: Clinical Practice Guidelines in Oncology - v.2.2006

Chemotherapy for Advanced or Metastatic Disease



ways patients with colorectal cancer can be treated. The NCCN guidelines are updated twice a year, which reflects how rapidly the data are changing in colon cancer. The changes to the NCCN guide-

lines occur faster than actual FDA approved indications can change.

The standard of care for Stage III colon cancer patients is FOLFOX (5-FU/leucovorin/oxali-

Exhibit 3: Median Overall Survival Correlates with Availability of All Effective Drugs

Author/Study	Year	% Pts w/3 drugs	OS (months)
Saltz	2000	5%	14.8
Douillard	2000	16%	7.4
de Gramont	2000	29%	16.2
Giacchetti	2000	60%	19.4
Tournigand	2001	68%	21.0
Grothey	2002	75%	21.4

Goal of therapy: expose all patients to all 3 active drugs - 5-FU/capecitabine, irinotecan, and oxaliplatin

Grothey A, et al. J Clin Oncol. 2004;22:1209-1214.

platin). There is an unequivocal advantage for patients receiving this regimen in terms of three- and five-year disease-free survival.³ Patients with Stage III colon cancer who are not candidates for this regimen, such as someone with peripheral neuropathy, are treated with capecitabine. About twenty-five percent of patients who receive a conventional six-month course of FOLFOX chemotherapy for their Stage III colon cancer will develop a residual peripheral neuropathy. Studies are also looking for ways to give this standard regimen while minimizing the long-term adverse effects of neuropathy.⁴

The first choice for therapy of an advanced disease is probably not nearly as important as thinking long-term. How do we expose patients to all the effective agents?

In a summary of the results of six large randomized studies looking at different chemotherapies in patients with stage IV colorectal cancer, patients who received all three active medications (5-FU or capecitabine, irinotecan, and oxaliplatin) had a better median survival compared to patients who did not receive all three agents (Exhibit 3).⁵ Although this was an imperfect analysis, it implies that being strategic and exposing colorectal cancer patients to multiple therapies is likely very important in maximizing their survival. The challenge is to do so without inducing excess toxicity. Analyses such as this have led many clinicians to abandon the classic thinking in cancer treatment, of giving a first line treatment, and then at progression, giving a second line treatment, and so on.

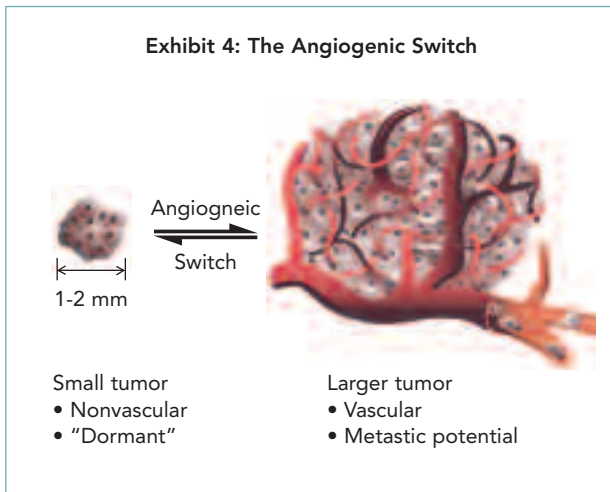
Treatment of Stage II patients is less clear. Stage

II patients appear to gain benefits from chemotherapy, but these benefits are much less than those seen in Stage III. This is primarily because Stage II colon cancer patients have a much better prognosis; the incremental advantage of chemotherapy is harder to demonstrate. Stage II patients get a very small incremental benefit from chemotherapy. Stage II colon cancer patients who receive chemotherapy in addition to surgical resection have an 81 percent likelihood of being cured.⁶ Those who do not get chemotherapy have an 80 percent likelihood of being cured. There is controversy whether Stage II patients should receive chemotherapy because there are risks from the treatment. The decision is a balancing act. One person's one percent is another person's great hope. In the current healthcare environment, it is a real dilemma for the oncologist who must decide whether to offer the option, or explain why a particular treatment is not an option because it would not be paid for.

Chemotherapy holidays, where treatment is stopped for a period of time, are another treatment strategy, which is being investigated. This is counter-intuitive to most patients. Many cancer patients have psychological problems with not being treated for their cancer. Their assumption is that if they take a hiatus from chemotherapy, the cancer will inevitably progress, they'll lose ground and their lives will be shortened. A very important consideration though, with a medication like oxaliplatin, which is incredibly effective, but causes cumulative peripheral neuropathy, is whether treatment can be interrupted and continue to be effective. The studies that have examined this type of strategy with oxaliplatin and irinotecan appear to indicate retention of efficacy.⁵ For the medical oncologist, it is difficult to convince patients to take a break. Again, this is a complexity of managing these patients.

Another area of complexity is determining who should and who should not receive a particular chemotherapy. There are tests for breast cancer patients that can help determine which medications they should receive. This is an area of ongoing study for colon cancer. There is one test that may be very important for predicting who should not receive irinotecan.⁷ Like many of new chemotherapy drugs, irinotecan is a pro-drug; it is not active when given, but is activated by normally occurring enzymes in the bloodstream. About 10 percent of the population have a defect in the enzyme that activates irinotecan and thus have difficulty producing the active drug molecule. Patients with this enzyme defect have a much greater likelihood of having severe toxicity and are

Exhibit 4: The Angiogenic Switch



much less likely to benefit from the drug. The package labeling of the product includes a recommendation that a reduced initial dose should be considered for those patients known to be homozygous for the defective gene (UGT-1A1). At this time, testing for the enzyme deficiency gene is not generally accepted as a standard, although there is a commercial assay available. This can lead to difficulty in obtaining managed care approval for alternative agents for irinotecan intolerant patients. A plan may deny the use of an alternative agent because the patient has not been treated with irinotecan, yet the patient has a known genetic defect that prevents safely being treated with irinotecan. The future of therapies for colon and other cancers is in selecting treatments based on the patient's genetic polymorphisms.

Three newer agents for colon cancer that are not chemotherapy, but rather biologic agents, are cetuximab, panitumumab, and bevacizumab. Cetuximab and panitumumab target the epidermal growth factor receptor (EGFR). Epidermal growth factor is one of the numerous pathways that appear to be integral to the cells developing the capacity to metastasize and spread. Interference with this pathway, so-called targeted therapy, has been the subject of a lot of research.

Cetuximab (Erbix[®]) is a chimeric antibody given each week that has been shown to be effective in combination with irinotecan, even in patients who failed irinotecan. The combination produces a twenty percent response rate.⁸ Cetuximab alone induces about a ten percent response rate.

Panitumumab (Vectibix[®]) is a human antibody. As opposed to cetuximab, it can be given once every other week. It targets the same receptor, EGFR. This class of medications causes acne, which can be severe. The interesting observation is that patients who have the worst acne may be those who get the most ben-

efit from the treatment. This agent costs approximately \$8000 a month compared to \$10,000 a month for cetuximab.

The cost of these agents is a major problem that oncologists, payers, and patients must face because the cost of these agents is not sustainable.

Both EGFR targeted agents are FDA labeled to be only used in patients with EGFR positive tumors, but several studies have shown that tumor status is not predictive of response. Many times the use of an EGFR inhibitor will be denied for not checking the EGFR status of patients' tumors. For the oncologist, the job is to determine what is best for the patients to offer the best outcome.

One of the hot topics in cancer therapy is anti-angiogenesis (i.e., turning off the blood supply to tumors). Tumors can grow to be a certain size without a blood supply and then they need a blood supply to flourish (Exhibit 4). Inhibiting growth of a tumor's blood supply can be done with vascular endothelial growth factor (VEGF) inhibitors. Bevacizumab (Avastin[®]) is a VEGF inhibitor.

Bevacizumab is approved for first and second line use in combination with chemotherapy. It has been studied in combination with most standard colon cancer chemotherapy regimens. Currently, a large number of patients with newly diagnosed advanced colorectal cancer are treated with FOLFOX and bevacizumab, which is a reasonable approach.

Bevacizumab's cost is \$7,000 per year and the agent causes significant side effects. In addition to causing hypertension, four percent of patients will get arterial thromboembolic events. One to two percent of patients will have bowel perforation. In patients who are having surgery, bevacizumab must be stopped six to eight weeks before the operation because it is thought to inhibit wound healing and would make patients predisposed to bleeding at the time of surgery.

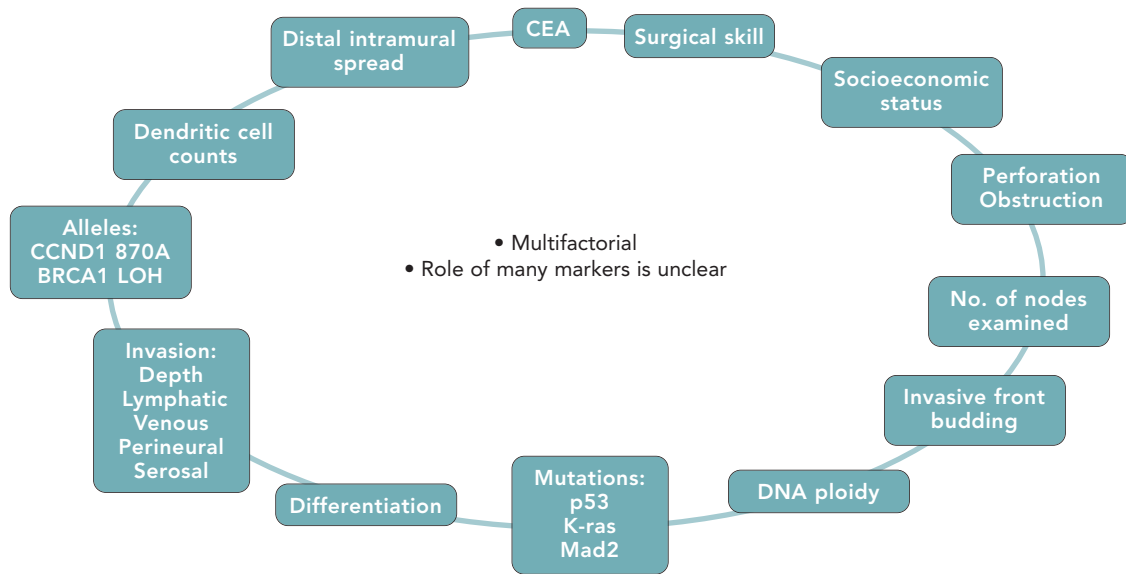
Bevacizumab adds efficacy to each chemotherapy regimen it has been studied with, but it appears to have a ceiling effect of only increasing progression free survival to ten months. This leads many experts to believe bevacizumab is an equalizer of chemotherapies across different populations.

Phase 2 studies combining irinotecan, an EGFR inhibitor (cetuximab) and a VEGF inhibitor (bevacizumab) are showing dramatic results of a thirty-eight percent response rate in patients who had already failed all prior chemotherapy. Although this Phase 2 data needs to be validated, combinations of EGFR and VEGF inhibitors are becoming a default treatment for patients who have failed everything else.

Figuring out who to treat with biologics is another hot area of research. Most contemporary

Exhibit 5: Factors that influence prognosis?

Variable prognosis is seen in patients with stage II and III disease.



chemotherapy studies are looking at factors that influence response and prognosis (Exhibit 5). An unanswered question is, “Can biologics be used together to make a bigger impact in patients than a single biologic alone?”

The advances in colon cancer therapy have been true advances. About fifteen years ago, the median survival for all patients with Stage IV colon cancer was about ten months. It did not matter what treatment they got. With all the advances, median survival is higher now.

A reasonable and rational approach for managed-care companies to take when determining coverage for colon cancer treatments is to follow the most recent updates of the NCCN guidelines. The NCCN guidelines are an expert, evidence-based consensus of what is and what is not appropriate therapy (i.e., the standard of care).

Conclusion

Every patient with colon cancer is a unique individual who may be treated differently. Achieving a cure or increasing survival is not just the question of which chemotherapy, but also how much chemotherapy, which agents or combination, and which adjunctive biologics? Many questions about optimal therapy remain unanswered. **JMCM**

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