Capecitabine in Colorectal Cancer

By John L. Marshall, MD [2]

Capecitabine (Xeloda) is the first orally available fluoropyrimidine approved for use in patients with cancer. It was initially approved for use in metastatic breast cancer, but significant data also support its use in the management of colorectal cancer.

Introduction

Fluorouracil (5-FU) has been the mainstay of treatment for colorectal cancer in the US for the past 40 years, primarily because no other agents with significant activity in colorectal cancer have been available. As a result, researchers focused on optimizing 5-FU therapy with two main strategies. The first was to add agents to 5-FU in a logical, biologically-based fashion that generates an enhanced anticancer response. Agents tested include leucovorin,[1] methotrexate (Folex, Mexate),[2,3] trimetrexate (Neutrexin),[4] PALA (Sparfosate sodium),[5] IUdR,[6] AZT,[7] interferon,[8] and many others. This strategy of biochemical modulation succeeded in generating improvements in response rates over single-agent 5-FU.[9]

The second major avenue of research altered the treatment schedule of 5-FU. Traditionally, 5-FU was administered as a bolus infusion and, consequently, was associated with a distinctive efficacy and side effect profile. However, when 5-FU is infused over a prolonged period, an alternate efficacy and toxicity profile emerges.[10] An extreme example of this strategy is the use of chronomodulated infusional 5-FU in an attempt to take advantage of diurnal variations in the metabolism of this agent.[11]

Bolus vs Prolonged Studies

Multiple studies, including meta-analyses, have been performed comparing bolus schedules of 5-FU with prolonged infusion schedules in colon cancer patients.[12,13] The evidence suggests that infusional schedules are less toxic, have higher response rates, and improve survival, compared with bolus schedules (Table 1). Major reasons for the lack of widespread use of continuous infusion 5-FU center around the inconvenience of prolonged infusion therapies and enhanced physician and patient care demands. The development of an orally bioavailable compound may circumvent these problems and lead to superior therapy for patients with colon cancer.

Because it is rapidly and inconsistently metabolized by dihydropyrimidine dehydrogenase (DPD), it is not feasible to use 5-FU orally. Several approaches have been pursued in an attempt to bypass DPD metabolism and create an orally bioavailable compound. One approach involves the use of agents that inhibit or compete directly with DPD and, in a sense, “level the playing field” so that 5-FU becomes orally bioavailable.[14,15]

The agent capecitabine (Xeloda) approaches this problem in a different way. This compound was designed to be resistant to DPD metabolism in its native form. However, through a series of enzymatic steps within the body and a final step within tumor cells, capecitabine is metabolized to become 5-FU.[16] Essentially, it is selectively activated within tumors as 5-FU, resulting in reduced systemic exposure and toxicity while maintaining high concentrations of intratumoral 5-FU.

There is considerable interest and debate surrounding the history of these oral 5-FU agents, and in this article, I will review the development and clinical experience of capecitabine in colorectal cancer. The successful evolution of these compounds has resulted in a more convenient method of administering 5-FU, a lower toxicity profile, and a significantly higher response rate in patients with metastatic colon cancer when compared to IV 5-FU.
Phase I Experience With Capecitabine

Three phase I trials of single-agent capecitabine using three different treatment schedules were performed in patients with a variety of malignant tumors. One involved prolonged continuous exposure using twice-daily dosing without interruptions.[17] A second used capecitabine alone in a 2-week-on and 1-week-off schedule.[18] The third used a similar intermittent schedule, but with the addition of leucovorin.[19] These studies found that the intermittent schedules allowed administration of higher doses of capecitabine but resulted in greater hand-foot syndrome. Diarrhea was reported as the dose-limiting toxicity in all treatment schedules.

An early clinical trial was performed in patients with colon cancer to prove that (1) the key activating enzyme, thymidine phosphorylase (TP), is indeed overexpressed within tumors as compared to normal tissues, and (2) that capecitabine is selectively activated within tumors resulting in higher 5-FU concentrations.[20] The study was designed to treat patients who were scheduled to undergo resection of either their primary colon cancer or a metastasis with a preoperative course of capecitabine 2500 mg/m$^2$ split into two daily doses for 5 to 7 days. Resections were performed within 12 hours after administration of the last dose.

Phase I Results

The resected specimens were then analyzed for levels of TP and 5-FU. Comparisons were made between tumor, and surrounding normal tissue, and plasma. The results strongly support the theory that capecitabine is selectively activated within tumors. First, tumor tissues markedly overexpress TP when compared to normal tissues (with the exception of normal liver, which also express high levels of TP). In an exact parallel, 5-FU levels were markedly higher in tumors compared to surrounding tissue and plasma, and again, the liver was the exception with fairly high levels of 5-FU. In fact, when the concentrations of 5-FU in tumor were compared to those within the plasma, a twenty-fold increase in 5-FU was found within tumors (Figure 1).

These data have been compared to similar analyses of IV 5-FU, which demonstrated that, following intravenous administration of 5-FU in colon cancer patients, there are higher concentrations of 5-FU in circulating plasma than in the tumor.[21] Therefore, this study strongly supported the importance of mechanisms of selective activation and increased delivery of 5-FU to the tumor.

Phase II Trial of Capecitabine in Colon Cancer

As reviewed above, several schedules emerged from the phase I trials, each having advantages and disadvantages. In order to define the optimum schedule to carry forward into more definitive phase III trials, a randomized phase II trial was performed comparing the three leading schedules of capecitabine in colorectal cancer.[22] A summary of the trial design is shown in Figure 2. This trial was performed in patients with metastatic colon cancer who had received no previous therapy. Patients were randomized to one of three schedules of capecitabine. The end points of the trial were response rates and toxicity, and an analysis for dose intensity was also performed.

Results demonstrated no difference in survival among the three treatment arms. However, there was significant improvement in time to disease progression in the patients who received capecitabine alone on an intermittent schedule as seen in Table 2. As predicted, the higher dose, intermittent schedules resulted in greater toxicity, particularly diarrhea and hand-foot syndrome, when compared with the lower-dose continuous infusion schedule. The intermittent schedule without leucovorin was selected for the phase III randomized trials based on the improved time to disease progression, the higher dose intensity, and the better therapeutic index associated with that regimen.

Phase III Trials of Capecitabine in Colorectal Cancer

Two phase III trials were conducted comparing capecitabine to intravenously administered 5-FU and leucovorin in patients with previously untreated metastatic colorectal cancer. One trial was
performed primarily in Europe[23] and the other, primarily in North America.[24] The design of the trials was identical and each was powered to show equivalence in overall response rate between capecitabine and IV 5-FU/leucovorin. Secondary objectives included a comparison of the toxicity, time to disease progression, overall survival, time to response, quality of life, and duration of response.

At the time the trials were designed, the standard of care for front-line treatment of metastatic colon cancer was the Mayo Clinic schedule of 5-FU and leucovorin[5-FU 425 mg/m$^2$ plus leucovorin 20 mg/m$^2$ administered intravenously for 5 days every 28 days. This regimen was therefore selected as the control arm for both of these studies. The standard criteria for phase III randomized trials in this disease population established eligibility for these studies. Tumor responses were analyzed by the investigators and by an independent group of radiologists, who were blinded. Tumor assessment was based on WHO criteria.

**Phase III Trial Performed in Europe, Taiwan, Australia, and Israel**

The demographics for this trial are summarized in Table 3. Both trial arms were evenly matched for all characteristics. Patients receiving capecitabine in this trial achieved an overall response rate of 26.6% compared to 17.9% for those receiving the Mayo Clinic 5-FU/leucovorin regimen ($P = 0.013$). However, when these responses were reviewed by an independent review committee, statistical significance was absent: the response rate for the capecitabine arm was 18.9% and 15% for those on the 5-FU/leucovorin arm. While there is a trend towards benefit in survival and time to progression with the use of capecitabine, it did not attain statistical significance.

Hand-foot syndrome was more common in patients treated with capecitabine, but mucositis and stomatitis were more common in the 5-FU/leucovorin regimen. Life-threatening grade 3/4 toxicities were less common in the capecitabine arm. Most prominent was the absence of fever/neutropenia in patients treated with capecitabine. Time to onset of the first grade 3/4 adverse events was more rapid with IV 5-FU/leucovorin than with capecitabine.

Significant differences in laboratory studies were seen between the two treatment arms with regard to myelosuppression and hyperbilirubinemia. A significantly greater number of episodes of grade 3/4 myelosuppression occurred in the IV 5-FU/leucovorin regimen, whereas increases in total bilirubin were seen in 23% of patients receiving capecitabine compared to 3% of IV 5-FU/leucovorin regimen patients. The elevation of bilirubin is similar to that seen with infusional 5-FU but the exact mechanism of this is unclear. The hyperbilirubinemia was mild and reversible.

This trial demonstrated a superior response rate with capecitabine; however, statistical significance was absent upon independent review. It also showed a time to disease progression and an overall survival rate equivalent to IV 5-FU. The use of capecitabine was associated with lower toxicity, including less neutropenia and stomatitis, but with a greater incidence of hand-foot syndrome.[23]

**Phase III Trial in United States, Canada, Mexico, and Brazil**

This trial was identical in design to the European trial. Eligibility and the treatment schedules were the same. A summary of the demographics is listed in Table 4. The arms were well balanced with a slightly greater number of patients who received prior adjuvant 5-FU in the IV 5-FU/leucovorin arm. The response rates reported in this study were 24.8% for the capecitabine arm and 15.5% for the IV 5-FU/leucovorin arm ($P = .005$). When these results were reviewed by the independent review committee, statistical significance was maintained and, in fact, improved with a response rate of 25.8% for the capecitabine arm and 11.6% for the 5-FU/leucovorin arm ($P = .0001$). However, there still was no difference in time to disease progression or overall survival between the two treatment arms.

The toxicity profile was similar to the European study with a greater degree of hand-foot syndrome observed in the capecitabine treatment arm and greater stomatitis observed in the 5-FU/leucovorin arm. Similar results were seen with regard to fever/neutropenia; however, the incidence was greater in the 5-FU/leucovorin arm. The time to onset of the first grade 3/4 adverse events was more rapid in the 5-FU/leucovorin arm, but elevations of bilirubin occurred more rapidly in the capecitabine arm.
The results of the study showed an improvement in response rate that was statistically significant but did not translate into a survival benefit. However, time to disease progression was equivalent between treatment arms and overall survival was similar. There was no difference in overall quality of life or global health status. Capecitabine was safe, resulting in fewer grade 3/4 toxicities compared with IV 5-FU/leucovorin.[24]

When data from the two clinical trials were pooled and analyzed, a statistically significant improvement in the overall response rate was observed by both the investigators and the independent review committee; however, there was no survival benefit as shown in Figure 3. Responses were greater with capecitabine regardless of tumor characteristics, such as tumor location, and prior treatment with adjuvant chemotherapy.

Significant dose reductions were implemented in the treatment arms of both studies: 42% of patients in the 5-FU/leucovorin arm required dose reductions and 33% in the capecitabine arm. Typically, dose reductions were made later with capecitabine, supporting the evidence that toxicities are not often seen on the first cycle of treatment but tend to occur during cycles 2 and 3. However, with the Mayo Clinic 5-FU /leucovorin regimen, toxicities are often observed during cycle 1. These data suggest that the doses used in both arms of this trial may be too high; in future studies, either lower doses or alternative schedules should be considered.

### Future Trials

#### Combinations

The development of capecitabine as a single agent in colorectal cancer has moved forward in an efficient and focused manner. Current research focuses on combination therapy with capecitabine and other active chemotherapeutic agents, such as CPT 11 and oxaliplatin. A series of phase I and II trials are underway to explore various combinations. It is hoped that the lower toxicity profile and improved response rates seen with capecitabine will translate into a more effective and less toxic combination therapy.

#### Adjuvant Therapy

Plans are underway for studies of capecitabine as adjuvant therapy of colorectal cancer (X-ACT study). However, there is concern about the use of capecitabine in the adjuvant setting because the drug must be activated by thymidine phosphorylase in order to be effective. It is possible that TP expression is somehow different in early microscopic metastatic disease compared to more advanced and visible metastatic disease. In my opinion, the role of TP expression must be defined for this drug before establishing it in the adjuvant setting.

#### Radiation Therapy

The use of orally available fluoropyrimidine compounds in combination with radiation therapy seems extremely logical. Patients undergoing radiation therapy experience a great deal of inconvenience already due to the daily nature of radiation therapy. Substantial evidence supports the use of continuous infusion 5-FU during radiation, although this strategy places an additional burden on the patient because of the need for a central venous access device and an infusion pump.

A number of trials are underway to define the dose and efficacy of capecitabine administered concurrently with radiation therapy. Radiation is believed to upregulate TP, and thus further enhance the conversion of capecitabine to 5-FU. It is possible that almost full doses of capecitabine can be delivered during radiation because normal tissues do not activate the drug and they are, therefore, not sensitized to it in the same degree as tumors are.

#### Financial Issues

The data presented in this review support the use of capecitabine in the management of advanced
colorectal cancer. There is greater patient convenience, less toxicity, and higher clinical efficacy with the oral agent as compared to IV chemotherapy. However, the administration of this agent still requires a significant amount of physician and nurse education, and patient monitoring.[25] Unfortunately, under the current reimbursement rules, there is no opportunity for physicians or their staff to be paid for the services.[26] If treatment is administered intravenously, then, in fact, there is reimbursement for patient education, although it is inadequate. This is clearly wrong and needs to be addressed on a national level.

**Conclusions**

Capecitabine is an effective, orally available agent for the treatment of colorectal cancer. It will likely play a large role in the future management of colon cancer with strong data supporting its use in the metastatic setting. Results of combination trials with other chemotherapeutic agents and radiation are eagerly awaited.

**Questions and Answers**

**Peter O’Dwyer, MD:** Dr. Marshall, what did the time to progression data show for both of the phase III studies you mentioned?

**John Marshall, MD:** They are basically right on top of each other. In the European study, I believe time to progression with capecitabine is a little longer than with the IV agent. In the US study, I think it is the opposite or very close.

**Peter Danenberg, MD:** I was just wondering if you compared survival and nonresponding to responding patients in each group.

**Dr. Marshall:** You really cannot do that. You can say the responders always lived longer than the nonresponders but that is not sufficient evidence that the treatment caused that. It could be biological differences.

**Paulo Hoff, MD:** I think what it shows is that we overrate response rate in solid tumors. Liquid tumors are different; you need a 50% response rate to make an impact. Look at the data from irinotecan (CPT-11[Camptosar]). There is a 15% response rate and you double your survival at 1 year. You go from 14% to 36%. We are talking about a billion cells. When you cut from a billion to 500 million, how much advantage would there be for the patient? That is why the FDA does not accept response rate as an indicator for approval because we don’t really know the significance of an objective response.

**Leonard Saltz, MD:** Does the response make a clinically detectable difference to a patient? In an asymptomatic patient with an ECOG 0 performance status, what you are doing is making pretty CT (computed tomography) scans. While that makes for a nice discussion and probably relief in the household that evening, it does not tangibly affect the patient’s physical well being. If you have a patient who is symptomatic from a bulky tumor and you shrink that bulky tumor and the patient becomes less symptomatic or asymptomatic, then I think there is a documentable or at least an identifiable tangible clinical benefit. If the patient is already feeling well, we have to ask what this therapy is adding, unless it is adding a survival advantage. And if the patient is not feeling well the question is can we make them feel better?

**Al Benson III, MD:** One of the difficulties is that if you look at trial after trial, the patients with the best outcomes are those with the least symptoms. So we are not having a huge impact on the symptomatic patient.

**Dr. Haller:** It is also difficult to do a quality-of-life analysis in a population patients that are 80% asymptomatic. In most instances, the only thing you can do is make them worse with treatment. With oral therapy, how much less worse are you going to make them than you would have with another drug?
Sunil Sharma, MD: I agree with the issue of response being overrated. As we move toward a cytostatic sort of paradigm, disease control is the issue. Is somebody looking at the older trials to see if there was truly a difference in the number of patients who had stable disease vs people who actually responded? I think that may be the critical point where you see a response rate difference but do not see a survival difference. Was there a difference in the number of people whose disease stabilized? This may have some biological connotations because if there was, for example, less angiogenesis in patients who stabilize, I think it may have future implications. If we are going to combine different cytostatic agents, one of the future strategies might be to actually reduce the dose of cytotoxic agents and add cytostatic agents to a point where the patient achieves optimal stability, rather than focusing on response, especially in asymptomatic patients. If you give people a highly toxic regimen, you may get a high response rate but it comes at the cost of toxicity.

References:
12. Meta-Analysis Group in Cancer: Efficacy of intravenous continuous infusion of fluorouracil


Source URL: http://www.physicianspractice.com/review-article/capecitabine-colorectal-cancer

Links: