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Current Developments in the Management of Colorectal Cancer

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What Is the Optimal Duration of Adjuvant Therapy in Colon Cancer?

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H&O Which patients with colon cancer require adjuvant therapy?

AS Patients who are considered to be at high risk for recurrence require adjuvant therapy. This generally means patients with stage III colon cancer, who by definition have lymph node involvement. Some patients with stage II colon cancer also require adjuvant therapy, however, and some patients with stage III colon cancer may not.

Specifically, patients with stage II colon cancer are at increased risk for recurrence if the tumor has penetrated through the wall of the colon. Conversely, patients who have early stage III cancers—with involvement of a single lymph node—may do better than patients with high-risk stage II disease. This overlapping of risk means that at some point, we will need to undertake a worldwide effort to update the classification scheme.

Other factors besides pathology, such as tumor genetics, also play a role in determining risk for recurrence.

H&O How effective is adjuvant therapy at preventing recurrence?

AS Adjuvant therapy decreases the risk for recurrence by approximately one-third. So, if the 3-year recurrence rate in patients with stage III disease is 40% without adjuvant treatment, chemotherapy will reduce that to approximately 25% to 30%. Multiple studies have demonstrated that adjuvant therapy improves disease-free survival (DFS) and overall survival in patients with colon cancer. We use nomograms—I tend to use the online nomograms from MD Anderson Cancer Center and Memorial Sloan Kettering Cancer Center. These allow us to plug in the relevant patient characteristics and get estimates of DFS with and without chemotherapy. I like to run the information through more than 1 nomogram because the answers can be a little different.

Patients react to this information in various ways. Some patients think that an absolute increase of 10% in the DFS rate does not justify going through chemotherapy, whereas others are willing to undergo chemotherapy for an increase of 3 or 4 percentage points. Much of this difference depends on comorbidities; someone with advanced heart disease or lung disease may be more harmed than helped by chemotherapy.

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H&O What are the standard chemotherapy regimens in colon cancer?

AS Some patients receive 5-fluorouracil (5-FU) or capecitabine alone, whereas others receive oxaliplatin in addition to a fluoropyrimidine. Oxaliplatin adds approximately 5 percentage points to the 3-year DFS rate, but it also adds toxicity. So again, that decision is made on a case-by-case basis. The ethos in colon cancer is different

from that in breast cancer, in which a more-intensive regimen is usually preferred even if it improves the DFS rate by just 2 percentage points.

For patients who are good candidates for oxaliplatin and are willing to accept the additional toxicity, we generally use either leucovorin/5-FU/oxaliplatin (FOLFOX) or capecitabine/oxaliplatin (CAPOX, sometimes called XELOX). Standard treatment lasts 6 months. In FOLFOX, we administer leucovorin and oxaliplatin intravenously in the clinic and send the patient home with a pump to administer the 5-FU. Patients generally return to the clinic after 2 days to have the pump removed, and treatments are done every 2 weeks for a total of 12 treatments. With CAPOX, patients receive a higher intravenous dose of oxaliplatin every 3 weeks, combined with oral capecitabine twice a day for the first 2 of every 3 weeks. Patients receive 8 cycles of treatment.

Although FOLFOX is used more often than CAPOX in the United States, I tend to favor CAPOX. I was involved in one of the first national trials in which CAPOX was given for advanced disease, so I am accustomed to using it. It is less cumbersome for patients because they come to the clinic every 3 weeks, as opposed to every 2 weeks, and there is no need for them to return to the clinic for pump removal. Of course, some patients prefer FOLFOX because they do not like taking pills. With CAPOX, we also have some concern about whether patients are taking all their pills. Both FOLFOX and CAPOX are used for advanced disease as well as for adjuvant treatment in earlier-stage disease.

H&O Can you describe what prompted the IDEA (International Duration Evaluation of Adjuvant Chemotherapy) Collaboration study?

AS We know that oxaliplatin can cause neurotoxicity that is cumulative and dose dependent, so it is important to avoid using more of it than is necessary. The IDEA Collaboration study looked at the question of whether 3 months of adjuvant treatment is noninferior to 6 months of adjuvant treatment for stage III colon cancer. This was a prospective trial that encompassed 6 studies in 12 countries. Dr Qian Shi of the Mayo Clinic in Rochester, Minnesota, presented the results at the 2017 annual meeting of the American Society of Clinical Oncology (ASCO).

When adjuvant therapy was first used in colon cancer many years ago, physicians gave 5-FU for 1 year, initially in combination with levamisol. The choice of 1 year was somewhat arbitrary at first, but it was shown to improve DFS. The recommended duration was changed to 6 months after another study found that 6 months of 5-FU worked as well as 12 months.

A study by Chau and colleagues that was conducted in the United Kingdom approximately 12 years ago compared 3 months vs 6 months of treatment, and 3 months seemed to work just as well. This was a small study, however, and the 5-FU was given over an extended period via infusion rather than as a bolus. Although the study was not definitive, the findings were intriguing and led to the hypothesis that 3 months of oxaliplatin treatment might be as effective as 6 months. The oxaliplatin trial began in Italy, and then other countries followed suit. It was Dr Daniel Sargent at the Mayo Clinic, who died last year, who originated the plan to combine data from 6 trials across a dozen countries.

H&O Which countries participated in the study?

AS The 6 studies were the SCOT (Short Course Oncology Treatment) trial from the United Kingdom, Denmark, Spain, Australia, Sweden, and New Zealand); the TOSCA (Three or Six Colon Adjuvant) trial from Italy; the Alliance/SWOG 80702 (Oxaliplatin, Leucovorin Calcium, and Fluorouracil With or Without Celecoxib in Treating Patients With Stage III Colon Cancer Previously Treated With Surgery) trial from the United States and Canada, led by Dr Jeffrey Meyerhardt of the Dana-Farber Cancer Institute in Boston, Massachusetts, and me; the IDEA France (Combination Chemotherapy for 3 Months or 6 Months in Treating Patients With Stage III Colon Cancer) trial from France; the ACHIEVE (Adjuvant Chemotherapy for Colon Cancer With High Evidence) trial from Japan; and the HORG (Hellenic Oncology Group) trial from Greece.

This pooled analysis was unique because the 6 component trials were set up with the intention of combining them later. The investigators agreed in advance on the design and data interpretation. The US component of the study has been under way for approximately 10 years. The original plan was for IDEA to enroll approximately 10,500 patients. The patients did better than we were anticipating, however; the relapse rate was lower than what we had predicted on the basis of older data. As a result, we needed to increase the enrollment by more than 2000 patients. The final number of patients in the study was 12,834.

H&O Did the prospective approach limit heterogeneity in IDEA?

AS The US arm of the study, which Jeff Meyerhardt and I led, required the use of FOLFOX because that is what most physicians here use. In the European arms, physicians could use either FOLFOX or CAPOX. The rate of CAPOX use varied among the countries, from 10% in IDEA France to 35% in TOSCA, 58% in HORG,

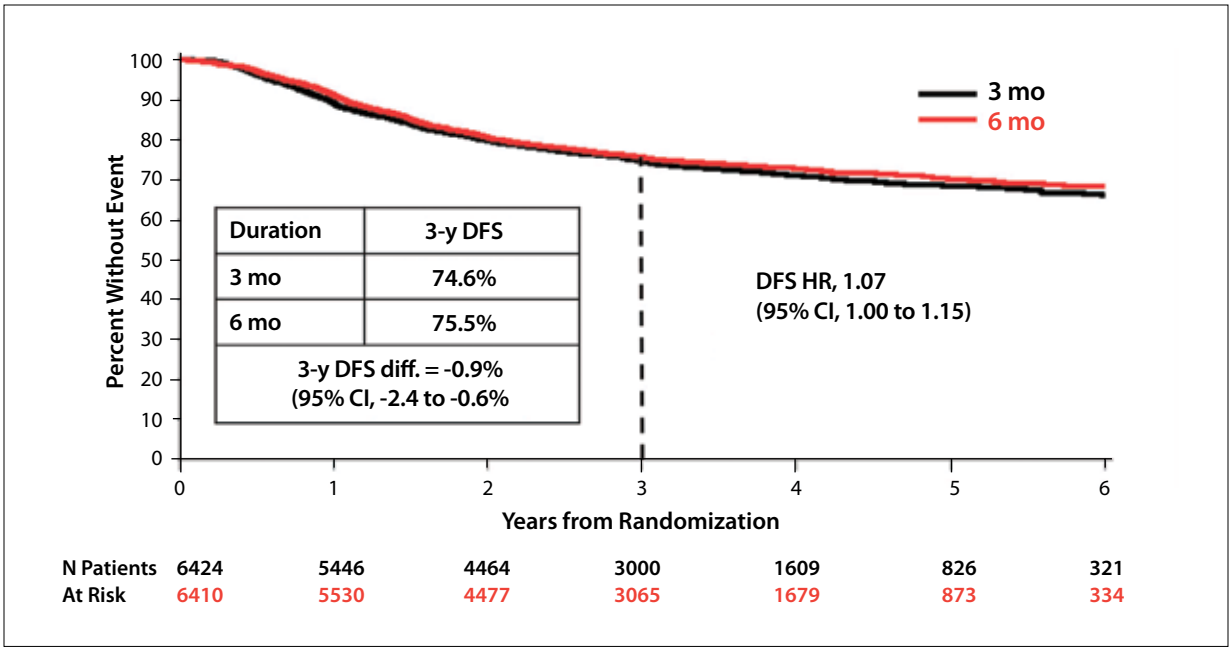

Figure. Primary analysis of disease-free survival in a modified intent-to-treat population. Source: Shi Q et al. ASCO abstract LBA1. *J Clin Oncol*. 2017;35(15)(suppl). Republished with permission of the author.

DFS, disease-free survival; HR, hazard ratio; mo, months; y, year.

67% in SCOT, and 75% in ACHIEVE. These variations in the regimen used became important because we found unexpected differences between the regimens.

Aside from the fact that there were more patients on CAPOX in some studies than in others, the patient characteristics and the results are about the same across the 6 studies. The tumor stage and number of lymph nodes involved were similar across countries, and we saw fairly uniform results across countries when we conducted analyses by higher vs lower risk for recurrence, or by FOLFOX vs CAPOX.

H&O What were the main results of the IDEA Collaboration study?

AS The results are somewhat complicated because this was a noninferiority study, which is a difficult design—far more complicated than a comparison of treatment A with treatment B. We needed a large number of patients to make the results statistically significant, and we designed rigorous statistics to look at that issue. We set an upper boundary for relative risk of 1.12, but unfortunately, this study did not reach the noninferiority boundary. On the other hand, the overall improvement between the 6-month and the 3-month arm was 0.9%. As small as the difference was, it did not meet the statistical goal that we had set; the 95% confidence interval for the 3-year DFS ranged from 0.6% better with 3 months of treatment to 2.4% better with 6 months of therapy.

The responses of the audience to this finding varied. One of the discussants at the session was Dr Cathy Eng of the MD Anderson Cancer Center. She said that because the study did not meet its goal, the standard of care should continue to be 6 months. An audience member, however, pointed out that the DFS curves for the 2 groups were nearly falling on top of each other, with a 0.9% difference in DFS at 3 years (Figure). Does someone really need 6 months of therapy, which clearly is more toxic than 3 months, for a difference of only 0.9%?

This is when we started to examine the factors that raise or lower risk, such as whether a tumor extends all the way through the colon wall and whether more than 1 lymph node is involved. In this context, we found small but important differences between FOLFOX and CAPOX. Among the low-risk patients (T1-T3N1) who received CAPOX, 3-year DFS was no worse and possibly better with 3 months of treatment than with 6 months (85% vs 83.1%)—which is difficult to explain. However, the low-risk patients who received FOLFOX for 6 months did slightly better than those who received it for 3 months (3-year DFS, 83.5% vs 81.9%).

Among the high-risk patients (T4 and/or N2), results were similar for those who received 3 months and those who received 6 months of CAPOX (3-year DFS, 64.1% vs 64.0%), but the results did not cross the noninferiority boundaries. In contrast, results were better with

6 than with 3 months of therapy for those who received FOLFOX (3-year DFS, 64.7% vs 61.5%).

H&O What did IDEA reveal about toxicity after 3 vs 6 months of treatment?

AS We saw a statistically significant difference in toxicity between the 2 groups, which is what we expected to see. The major toxicity of concern with oxaliplatin is neurotoxicity; a study by André and colleagues that was published in the *Journal of Clinical Oncology* in 2009 found a 12.5% rate of grade 3 neuropathy with 6 months of FOLFOX.

In IDEA, there was a statistically significant decrease in the rates of grades 3 and 4 neurotoxicity when the length of treatment changed from 6 to 3 months (from 16% to 3% with FOLFOX and from 9% to 3% with CAPOX). There was also a statistically significant decrease in the rate of grade 2 neurotoxicity when the length of treatment changed from 6 to 3 months (from 32% to 14% with FOLFOX and from 36% to 12% with CAPOX). If you combine the statistics for grades 2, 3, and 4 neurotoxicity, the risk decreased from 48% to 17% with FOLFOX and from 45% to 15% with CAPOX. These are very striking differences. When patients experience significant numbness, tingling, or pain in their fingers and toes, we lower the medication dose, but this does not always eliminate the problem. What's more, neurotoxicity is an unusual side effect in that it can persist after treatment ends. For example, I have one patient who needs medication for severe toxicity 5 years after oxaliplatin treatment.

> We found that the high-risk patients did not do very well whether they had 3 or 6 months of treatment.

Many patients are willing to deal with neurotoxicity for a couple of months until treatment has been completed, but the physician needs to explain that the condition may not go away or even worsen after the medication regimen ends. Long-term neurotoxicity is not something that most patients will want to live with.

Other side effects of chemotherapy include infections and low blood counts, which occur relatively early in the course of treatment and can be fatal. The rate of death due to chemotherapy in our study was approximately 1%.

H&O How have the results of the IDEA Collaboration study altered what you recommend for patients?

AS We now recommend 3 months of chemotherapy for patients with T1-T3N1 stage III colon cancer. This lower-risk category comprises approximately 60% of the patients with stage III disease. The chemotherapy regimen can be either FOLFOX or CAPOX.

IDEA was not specifically designed to compare FOLFOX vs CAPOX, but we certainly had a lot of patients in each group in the study. The evidence suggests that patients do slightly better with CAPOX; on average they do approximately 2 or 3 percentage points better. I had often used CAPOX for my off-study patients, and the results of IDEA have encouraged me to use CAPOX more often.

Regarding the higher-risk patients—those with T4 tumors that penetrate all the way through the colon wall or who have at least 4 positive lymph nodes—the advice becomes more complicated.

For the patients on FOLFOX, treatment for 3 months was inferior by 3.2 percentage points. So the question becomes, is it worth sacrificing 3.2 percentage points in 3-year DFS for a large reduction in toxicity? The answer is in part determined by patient preference. One reasonable approach is to begin with 3 months of treatment and then reevaluate.

Another question is whether to choose CAPOX over FOLFOX in these higher-risk patients because they did equally well with 3 vs 6 months of CAPOX. The other investigators and I have debated about why that is the case, but CAPOX did look a little bit better than FOLFOX. I recently advised a patient with higher-risk stage III cancer who came to me for a second opinion that 3 months of CAPOX was a reasonable approach.

These are the types of discussions we are having with patients at our institute. Numerous people in the community had been awaiting these results; in some cases, they had already started treatment and needed to decide whether they would continue past 3 months. They were aware that the data were being presented and discussed in June at the ASCO meeting. We are continuing to debate their significance, and we are in the process of writing the paper that will summarize our results.

We are never going to see a study in which patients are randomly assigned to CAPOX or FOLFOX. We would not be able to enroll thousands of patients over many years, which is what we would need to do to detect a difference of 2 or 3 percentage points. The IDEA Collaboration study was difficult enough to conduct, and it's the best study we have that looks at neoadjuvant therapy in these patients.

H&O Is there anything else that you would like to add?

AS We found that the high-risk patients did not do very well whether they had 3 or 6 months of treatment. The 3-year DFS rate was approximately 64% no matter what regimen we used, which is unacceptable. We can consider the IDEA study to be a baseline for investigating ways to treat high-risk patients more effectively. What has been tried so far—such as adding cetuximab (Erbitux, Lilly) to treatment—has not worked.

As for other studies, an ongoing double-blind trial (Oxaliplatin, Leucovorin Calcium, and Fluorouracil With or Without Celecoxib in Treating Patients With Stage III Colon Cancer Previously Treated With Surgery; NCT01150045) is looking at whether celecoxib can improve DFS in these patients. We should have results from this trial in another year and a half. Other retrospective trials, including one by Chan and colleagues, have found an association between aspirin use and better outcomes.

Finally, as Dr Jeanne Tie explained in a presentation at the 2016 ASCO meeting, we are studying whether circulating tumor DNA in patients with stage II colon cancer can be used to predict whether some of these patients are at high risk and will benefit from chemotherapy.

Disclosure

Dr Shields has no relevant disclosures.

Suggested Readings

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