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Current Developments in the Management of Colorectal Cancer

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Determining the Optimal Duration of Adjuvant Therapy in Colon Cancer

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H&O Which patients with colon cancer are eligible for adjuvant therapy?

JM Patients with colon cancer are eligible for adjuvant therapy if they have stage III disease or, in some cases, if they have stage II disease. Stage III disease is relatively straightforward; these patients have positive lymph nodes around the primary tumor, and the evidence is consistent for the benefit of adjuvant therapy after surgery. Stage II disease is more complicated; patients with high-risk features are considered more likely to benefit, whereas those with lower-risk features are less likely to benefit. Because the data are less definitive for adjuvant therapy in stage II disease, a discussion with the patient about the preferred approach is required.

H&O What features do you take into consideration when determining risk in patients with stage II disease?

JM Several pathologic features are prognostic for increased likelihood of recurrence in stage II disease, including T4 level of invasion through the bowel wall, inadequate lymph node sampling, clinical bowel obstruction or perforation, and poorly differentiated tumor. Although these features are prognostic, their predictive value related to the use of adjuvant therapy is less clear. Despite this lack of clarity, many of us will offer adjuvant therapy to patients with high-risk stage II features.

One important factor that has both prognostic and predictive value in stage II disease is microsatellite instability (MSI). If a patient has MSI-high stage II disease, particularly without high-risk features, adjuvant therapy—especially with a fluoropyrimidine alone—is not beneficial. We do not have good data at this point to determine whether other molecular features, such as *RAS* and *BRAF* mutations, should be factored into decisions regarding the use of adjuvant therapy. Looking specifically at adjuvant treatment with immunotherapy, no data as of yet have shown a benefit, although ongoing trials are looking at the addition of immunotherapy to chemotherapy in patients with MSI-H stage III disease.

H&O What are the standard adjuvant regimens used in these patients?

JM All of the regimens include an intravenous or oral fluoropyrimidine, so either 5-fluorouracil (5-FU, used in combination with leucovorin) or capecitabine. If the patient has stage III disease or high-risk stage II disease, the oncologist will consider adding oxaliplatin, which is generally administered with leucovorin plus 5-FU (FOLFOX) or with capecitabine (CAPOX, sometimes called XELOX).

H&O How effective are these regimens?

JM We have clear data regarding patients with stage III disease. If we look at people with stage III colon cancer as a group, 50% will remain disease-free in the long term with surgery alone. If we add a fluoropyrimidine, we are able to boost the disease-free rate to approximately 65%, and if we add oxaliplatin, it goes up to about 72%. The statistics vary according to how far the tumor penetrates the bowel wall and how many lymph nodes are involved. The chance that someone with lower-risk stage III disease will remain disease-free is closer to 80%. People who have higher-risk features, such as T4 disease (or extensive lymph node involvement), are going to have a rate of disease-free survival (DFS) much lower than 72%, even with the use of a fluoropyrimidine and oxaliplatin.

H&O What are the advantages of the shorter regimen vs the longer one?

JM The shorter regimen, which lasts for 3 rather than 6 months, has been studied primarily in patients receiving a fluoropyrimidine plus oxaliplatin. One advantage of a shorter regimen is a reduced likelihood and severity of cumulative neuropathy from the oxaliplatin. The longer the duration of oxaliplatin, the more likely the development of cumulative neuropathy, which can linger after treatment ends—sometimes for months or even years—and may never fully resolve. Longer regimens also mean higher costs, which encompass financial expenses as well as the inconvenience of having to return to the health care facility for treatment.

H&O Can you discuss the findings of IDEA?

JM The IDEA (International Duration Evaluation of Adjuvant Chemotherapy) collaboration encompassed 6 trials. I was one of the investigators in the US trial, CALGB/SWOG 80702. In addition, a trial was conducted in each of the following countries: the United Kingdom, Greece, Italy, France, and Japan; all them compared 3 vs 6 months of a fluoropyrimidine plus oxaliplatin. CAPOX or FOLFOX was allowed in 5 of the trials, whereas CALGB/SWOG 80702 allowed only FOLFOX. The main analysis of IDEA, which we presented at the 2017 American Society of Clinical Oncology (ASCO) Annual Meeting and later published in the *New England Journal of Medicine*, was specifically for stage III disease. This analysis of 12,834 patients found that although the absolute difference between the 3-year DFS rates in the 2 groups was just 0.9%, this did not reach the noninferiority boundary. Although we could not declare 3 months to be statistically noninferior to 6 months for all patients, clinically the difference was very small, and this fact should be considered when duration of therapy is discussed with patients. Another 2 conclusions were drawn from the data. First, for patients treated with CAPOX, 3 months of therapy was statistically noninferior to 6 months. Second, for patients with lower-risk stage III disease (specifically those with T1, T2, or T3 disease and ≤3 positive lymph nodes), 3 months of therapy was noninferior.

The main update, which was presented at the 2020 ASCO Virtual Scientific Program and has since been published in *Lancet Oncology*, was based on 6 years of follow-up and included 5-year overall survival (OS) data on 12,835 patients. The results were pretty similar to those with DFS when the entire group was considered; 3 months of chemotherapy was not considered noninferior to 6 months of chemotherapy. When the CAPOX group specifically was considered, however, the 3-month regimen was statistically noninferior to the 6-month regimen (82.1% vs 81.2%, respectively). Another point was that even in the entire group, the 5-year OS rate was 82.4% with 3 months of therapy and 82.8% with 6 months of therapy. Even though the difference between the 2 regimens did not meet the requirement for statistical noninferiority, it was extremely small—a difference in absolute risk of just 0.4%.

H&O Can you discuss the analysis of stage II patients in IDEA?

JM Patients with high-risk stage II disease were included in 4 of the trials, and subsequent analyses have looked specifically at these patients. The most recent is the analysis by Iveson and colleagues, which looked at 3273 patients within IDEA who had stage II disease and appeared in the *Journal of Clinical Oncology* earlier this year. As with stage III disease, 3 months of treatment was not shown to be noninferior to 6 months of treatment in the general group of patients; the 5-year DFS rates were 80.7% vs 83.9%, respectively. Among those who received CAPOX, however, 3 months of treatment was shown to be noninferior to 6 months of treatment. So, for a patient with high-risk stage II colon cancer, 3 months of CAPOX is an appropriate regimen.

H&O Have the more recent analyses affected practice?

JM These data pretty much confirmed what had been reported several years ago and extended those findings from DFS to OS. It also confirmed that for the vast majority of patients, 3 months of therapy is clinically just as good as 6 months of therapy. Patients who are at particularly high risk might benefit from extending to

6 months of adjuvant therapy, but the benefit from the additional 3 months of treatment is small.

When the IDEA analysis first came out, the data were difficult to grasp because the analysis was designed around the statistical approach of noninferiority. I do think that over time, we have seen a greater acceptance of the concept of risk-stratifying patients with stage III disease and considering which of them would be appropriate candidates for shorter-duration therapy and which ones are at higher risk for recurrence.

We want to know whether factoring in the molecular subtype of a colon cancer—for example, a *BRAF*-mutated or an MSI-high tumor—can help us determine the optimal duration of adjuvant treatment for each patient.

H&O What questions remain to be answered when it comes to duration of therapy in colon cancer?

JM Right now, risk stratification is based on pathologic features, specifically T stage and N stage. We want to know whether factoring in the molecular subtype of a colon cancer—for example, a *BRAF*-mutated or an MSI-high tumor—can help us determine the optimal duration of adjuvant treatment for each patient. Many of the trials collected tumor blocks, and these analyses are ongoing now, so we hope to have more data in the near future.

H&O What trials are currently looking at adjuvant therapy in colon cancer?

JM Several ongoing trials are looking at immunotherapy in patients with MSI-high tumors. The Alliance for Clinical Trials in Oncology is recruiting patients for a phase 3 trial, called ATOMIC, that is being led by Dr Frank Sinicrope (NCT02912559). This trial, which is looking specifically at MSI-high stage III tumors, is studying whether adding the programmed death ligand 1 inhibitor atezolizumab (Tecentriq, Genentech) can improve DFS. In addition, a trial in the United Kingdom is studying the use of immunotherapy after standard chemotherapy in patients with MSI-high tumors. Multiple ongoing trials are looking at adding aspirin, either during or after the completion of chemotherapy (NCT02607072, NCT00002527, NCT02467582, NCT00565708, NCT02945033, NCT02804815, NCT03464305, NCT02301286, and NCT02647099). A trial from the Canadian Cancer Trials Group, which is being led by Dr Kerry Courneya, is studying the benefit of physical activity after standard treatment for patients with high-risk stage II or stage III cancers (NCT00819208). In addition, multiple trials are open to accrual as well as in development to determine how to utilize circulating tumor DNA in decision making regarding the use of adjuvant therapy and its intensity, including COBRA (NCT04068103), PEGASUS (NCT04259944), and CIRCULATE (NCT04120701 and NCT04089631).

Disclosures

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Suggested Readings

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