ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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Colorectal Cancer In Focus

Adjuvant Chemotherapy for Stage II and III Colorectal Cancer

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H&O What are the factors that are considered when deciding who should or should not receive adjuvant chemotherapy?

AB The discussion is different when talking about colon cancer and rectal cancer, so that distinction needs to be made first. Generally, for stage II patients, it is important to review the risk versus the benefit of adjuvant chemotherapy for the average-risk patient because the benefit of adjuvant therapy is very low.

In terms of adjuvant therapy, analyzing the tumor for mismatch repair, in particular deficient mismatch repair or microsatellite instability (MSI), should be done. Although these are different types of testing—mismatch repair is done by immunohistochemistry whereas MSI is performed by polymerase chain reaction—biologically they are comparable. Retrospective database analyses have shown that patients with deficient mismatch repair not only do not benefit from fluorouracil chemotherapy, but that it may be harmful to them. Thus, it is important to test for microsatellite instability, particularly in stage II patients.

For stage III patients, the role of MSI and the use of chemotherapy are not really defined. Although stage III patients with tumors that have a high level of MSI (MSI-H) or deficient mismatch repair may have a better prognosis, the retrospective data suggest that these patients might not benefit from fluorouracil. At this point, we do not know how well these patients would respond to a standard adjuvant regimen such as fluorouracil, leucovorin, and oxaliplatin (FOLFOX) or capecitabine plus oxaliplatin (CAPOX). In the MSI-H patients, we should consider genetic counseling. This raises issues such as whether all stage III patients need adjuvant chemotherapy. Unfortunately, we cannot yet segregate those who only need surgery from those who could benefit from chemotherapy. Therefore the current standard of care is to offer all stage III patients adjuvant chemotherapy.

H&O What do the guidelines suggest in terms of treatment?

AB For colon cancer, we advise oncologists to follow the American Society of Clinical Oncology and National Comprehensive Cancer Network guidelines. For stage II colon cancer, the guidelines emphasize the importance of talking with the individual patient about the potential risk of recurrence and the potential benefit of adjuvant chemotherapy. Physicians are urged to take a very thorough family history to ensure that patients are not at potential risk for an inherited colorectal cancer (ie, hereditary non-polyposis colon cancer [Lynch Syndrome]). For example, if we are presented with a patient under 50 years of age who has a relative with colon cancer, that would be an important signal to consider genetic counseling. This is very important because for patients with inherited colon cancer, if they are stage II, they have a better overall prognosis and

should not receive adjuvant chemotherapy. Surveillance for a second primary must be different than for the patients who do not have an inherited form of colon cancer, because second primaries can develop much more quickly in these patients compared to sporadic colon cancer patients.

H&O What have recent studies found in regard to treatment for stage II/III colorectal cancer?

AB The MOSAIC (Multicentre International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer) study is a large clinical trial that evaluated FOLFOX versus 5-FU in stage II and III colon cancer, which found that stage II patients did not benefit from FOLFOX compared to 5-FU. Hence, if there is a decision to give adjuvant chemotherapy to an average-risk stage II patient, the choice of regimen should be 5-FU and not FOLFOX, as FOLFOX does not appear to add benefit but does add toxicity. FOLFOX is a standard of care for stage III patients as noted in the MOSAIC trial.

H&O Are there any specific high-risk features for which chemotherapy should be considered?

AB For the high-risk stage II patients, who are the minority, there are a number of factors, mostly pathologic, that are analyzed. One such factor is T4 tumors. Patients with T4 tumors are at a higher risk for recurrence, and therefore many oncologists will choose to treat those patients. In the MOSAIC study, those patients who were high risk appeared to derive more benefit from FOLFOX compared to single-agent 5-FU in terms of progression-free survival, although this observation will require further confirmation. Other factors include perineural invasion, lymphovascular invasion, obstruction, and grade of tumor, although caution must be taken when looking at grade, because patients with high-grade tumors may also have a better prognosis if they have MSI-H tumors, for example. The number of lymph nodes sampled is another factor, although there is not a set number that determines treatment/prognosis. Generally, if a patient has fewer than 12 lymph nodes evaluated, he or she is considered inadequately staged and at higher risk for recurrence.

There has been a lot of work recently assessing gene signatures as prognostic and predictive markers. The problem with gene signatures is that at this point we cannot use them to predict who will actually benefit from adjuvant therapy. The hope is that over time, we will develop gene signatures that will help predict benefit for both stage II and III patients, and that will not only make it easier to select patients for adjuvant therapy but will tell us which adjuvant therapeutic agent should be used.

H&O Are there any studies evaluating chemotherapy in stage II/III CRC?

AB The Eastern Cooperative Oncology Group E5202 trial is evaluating over 2,400 patients whose treatment regimen was determined by their marker status. The patients were stratified by MSI-H and 18q loss of heterozygosity. Patients who fell into the low-risk category were observed, and those who fell into the high-risk category were randomized to FOLFOX with or without bevacizumab. Initial data from this study are expected within the next few years. There have been 2 published studies, both including stage II and stage III colon cancer patients (National Surgical Adjuvant Breast and Bowel Project C08 and AVANT [Avastin Adjuvant]) that demonstrated that the addition of bevacizumab adds no benefit over and above FOLFOX. Currently, the largest stage III effort is evaluating 3 months versus 6 months (6 cycles vs 12 cycles) of FOLFOX chemotherapy including the US National Cancer Institute Gastrointestinal Intergroup trial. If this trial meets its accrual, we will be able to combine data sets with similar trials being conducted around the world to determine the benefit of shorter course chemotherapy, thus avoiding toxicities from more prolonged exposure as is the current standard.

H&O What role do molecular markers play in research and development in stage II and III colorectal cancer?

AB In general, the data supporting the use of KRAS and MSI does encourage further investigation into molecular markers and, as previously mentioned, gene signatures are being looked at to determine their prognostic and predictive utility. Without question, the goal is to develop a biologic strategy with which we can identify patients who are at significant risk for recurrence and concurrently create a profile that would predict benefit from an adjuvant therapy approach. Further refining this strategy would allow us to understand biologic pathways for which we could develop drugs that would more specifically target pathways. One way to do this is to identify circulating tumor cells and determine whether those cells are more likely to include a pathway configuration that would result in development of metastases and thus inform selective drug development.

Overall, the emphasis is on understanding the biology of human colorectal cancers. When we look at therapeutic strategies to treat colorectal cancer, it has been a fairly unrefined process. One of the challenges is that the primary tumor may not have the same molecular

features as the tumor cells that metastasize. Furthermore, tumor cells that metastasize may also be a heterogeneous composition of cells, and therefore it is difficult to tease out what the targets need to be for a mixed population of cells. Thus, it is a daunting challenge, but one that has to be addressed in the discussion of molecular markers.

In the adjuvant setting, the goal is to segregate out more effectively those who will recur and those who will not, and then to find a strategy to link the tumor biology with the prediction of benefit from therapy.

H&O Are there any challenges when deciding on treatment in stage II and III colorectal cancer patients?

AB It is a challenge for patients to understand risk versus benefit. People can have different perspectives; for example, if we tell a patient that he or she has a 90% chance of not recurring, that might be viewed differently than if we say that he or she has a 10% chance of recurring. How patients view their risks, overall prognosis, and the percentage of benefit from additional interventions can vary tremendously with the individual. These are concepts that can be difficult to explain, particularly because it is unknown if the patient would in fact benefit from a therapeutic intervention (ie, we may use prognostic factors to frame the discussion of recurrence risk; however, we do not have the ability at this time to predict benefit from therapy even if we tell the individual he or she is at a higher risk for recurrence).

Suggested Readings

Clinicaltrials.gov. Oxaliplatin, leucovorin, and fluorouracil with or without bevacizumab in treating patients who have undergone surgery for stage II colon cancer. Identifier: NCT00217737. http://clinicaltrials.gov/ct2/show/NCT00217737.

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