E5202: The GI Intergroup Strategy for Stage II Colon Cancer Patients

The quest for individualized patient therapy

by Al B. Benson III, MD, FACP

Trial Name

Phase III Randomized Study of Oxaliplatin, Leucovorin Calcium, and Fluorouracil With Versus Without Bevacizumab in Patients with Resected Stage II Colon Cancer and at High Risk for Recurrence Based on Molecular Markers (ECOG-E5202)

Principal Investigators

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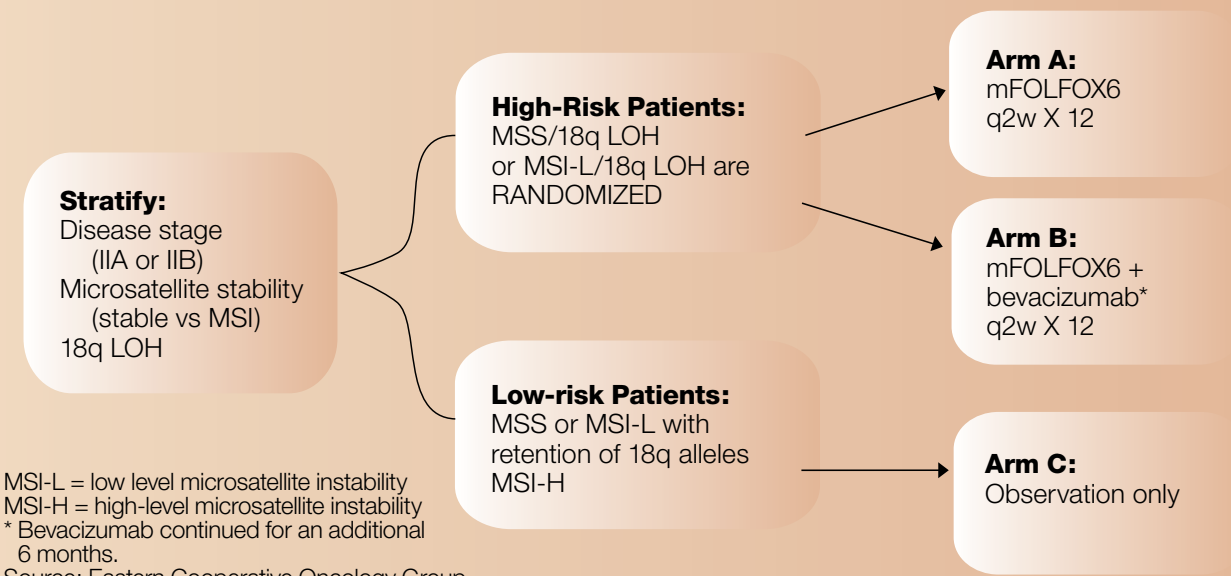
Over the last six years, treatment opportunities for patients with colorectal cancer have evolved rapidly. The introduction of irinotecan, oxaliplatin, capecitabine, bevacizumab, cetuximab and, most recently, panitumumab offers new hope for patients. At the same time, the evolution of treatment options has generated a growing list of questions about optimal treatment schedules and sequences.

Ideally, a patient's optimal treatment choice would be determined by individual biological characteristics of both the patient and the tumor. This quest for an individualized treatment approach has been hindered by the paucity of data linking biologic factors to efficacy.

Currently, stage remains the most important prognostic factor, with important differences in survival among subsets of patients with Stage II or Stage III colon cancer. However, advances in technology are greatly enhancing the study of colon cancer biology, and are offering new opportunities to design clinical trials that investigate other prognostic and predictive markers.

Case in point: Current controversy surrounding adjuvant therapy for Stage II colon cancer. Although it is universally accepted that most Stage III colon cancer patients should be offered adjuvant therapy, the treatment of the Stage II patient remains controversial. Few would argue that there is no fundamental biological difference to suggest that therapy would not benefit either a Stage II or Stage III patient; however, the routine treatment of all Stage II patients results in a high percentage of individuals receiving therapy that offers no further benefit beyond surgery alone. After an extensive analysis of randomized clinical trials, the Cancer Care Ontario Program and the American Society of Clinical Oncology (ASCO) have concluded that the routine use of adjuvant chemotherapy for Stage II colon cancer patients cannot be recommended based on the limited benefit of intervention for the overall Stage II population.[1,2] It is recommended that a discussion of risk versus benefit prior to making a treatment decision occur between the patient and physician. Although risk factors, including pre-operative CEA

Figure 1: E5202 Trial Schema



MSI-L = low level microsatellite instability
MSI-H = high-level microsatellite instability
* Bevacizumab continued for an additional 6 months.
Source: Eastern Cooperative Oncology Group.

(carcinoembryonic antigen level), lymphatic and/or vascular invasion, and tumor grade are potential indicators of risk, at this time they do not correlate with treatment benefit. Therefore, it is critical to design clinical trials that examine assessment of risk with a defined treatment approach to determine what correlation, if any, exists.

Why E5202 is Important

E5202 represents the largest Stage II colon cancer trial attempted in the United States that, unlike previous trials which included Stage II patients, will have sufficient numbers of patients to answer select biologic and treatment questions. E5202 is also the first large randomized colon cancer trial to use a patient's tumor molecular profile to determine risk and treatment strategy.

Retrospective subset analyses have suggested the favorable prognostic significance of colon tumor microsatellite instability (MSI) and retention of the 18q allele. For example, a retrospective analysis conducted by the Eastern Cooperative Oncology Group (ECOG) included patients who were treated with adjuvant 5-FU-based regimens in two United States GI Intergroup clinical trials as an attempt to define MSI and 18q LOH (loss of heterozygosity) as potential molecular predictors of survival after adjuvant chemotherapy. This study demonstrated a significant five-year overall survival advantage for Stage III patients who retained 18q alleles and received 5-FU-based chemotherapy compared to those with 18q LOH (74 percent vs 50 percent; relative risk of death with 18q LOH 2.75; p = 0.006).[3] The study also showed a five-year survival advantage for patients whose tumors had MSI-H in the presence of TGF-ß1R2 mutation compared to those with microsatellite-stable tumors (74 percent vs 46 percent; relative risk of death 2.90; p = 0.03). These retrospective data support the design of a prospective trial which determines a patient's risk of tumor recurrence based on the individual's own tumor molecular profile and correlates such with prognosis (E5202).

In another retrospective analysis, there was no survival advantage for patients with MSI-H who received adjuvant chemotherapy, whereas patients with MSS or MSI-L tumors had improved overall survival with adjuvant therapy.[4]

Figure 1 outlines the schema for E5202. The randomization of high-risk patients to receive FOLFOX with or without bevacizumab is consistent with the current Intergroup clinical trial design for colon and rectal cancer adjuvant therapy. The accrual goal is 3,610 patients. An important study-specific hypothesis is that the lowest-risk group of Stage II patients will have a five-year survival of approximately 90 percent without adjuvant therapy, whereas the high-risk Stage II patients will have a 60 percent five-year survival.

The importance of E5202 is multifactorial. If the trial hypotheses are correct, E5202 will:

- More clearly define a low-risk population that will not require adjuvant chemotherapy
- Determine the impact on survival of FOLFOX with or without bevacizumab for a high-risk Stage II population of patients
- Provide a comprehensive evaluation of a host of clinical pathologic and laboratory-based risk factors by multivariate analysis
- Create the largest well-documented tumor bank of Stage II colon cancer patients, promoting future analysis of other factors including future evaluation of gene signatures as prognostic and predictive markers.

E5202 has been designated a high-priority study by the National Cancer Institute (NCI) and the Centers for Medicare & Medicaid Services (CMS). In addition, ACOSOG surgeons will receive credit for identifying patients for the trial. This trial is covered under the Medicare Anti-Cancer Drug National Coverage Decision (*www.cancer.gov/clinicaltrials/ developments/NCD179N).*

Both surgeons and oncologists are encouraged to strongly support the accrual of patients to E5202 as a major step forward in the quest to develop individualized patient therapy based on specific biologic tumor characteristics. For more information on E5202 go to *http://www.cancer.gov/clinicaltrials/ECOG-E5202.*

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