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Adjuvant Chemotherapy of Stage III Colon Cancer

Al B. Benson III

Over the past two decades there have been notable advances in our understanding of what constitutes optimal adjuvant chemotherapy in patients with stage III colon cancer. Retrospective analyses of stratification by nodal status, T stage, and disease grade have shown marked differences in survival among patients with stage III disease, indicating the need for prospective stratification in clinical trials of adjuvant therapy. Similarly, analysis of the effects of such genetic/biologic properties as 18q loss of heterozygosity and microsatellite instability has shown marked differences in survival outcome with adjuvant therapy, prompting incorporation of investigation of potential prognostic markers in clinical trials. Recent randomized trials in stage III disease have shown that oxaliplatin combined with 5-fluorouracil (5-FU) and leucovorin (FOLFOX) is superior to the infusional leucovorin/5-FU (LV5FU2) regimen, that oral capecitabine is at least equivalent to bolus 5-FU/LV, and that irinotecan and 5-FU/LV (IFL) is not superior to bolus 5-FU/LV. Ongoing studies are likely to provide information that will markedly improve the ability to select optimal adjuvant therapy for individual patients.
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Approximately 55% of all newly diagnosed colorectal cancer patients present with stage II or stage III disease, and are thus potential candidates for adjuvant chemotherapy. There have been many changes in what is considered to be optimal adjuvant chemotherapy over the past two decades. Indeed, it has recently become apparent that improved risk stratification among patients with stage III disease is necessary to accurately determine effects of adjuvant therapy in this setting and to permit formulation of optimal treatment strategies.

Risk Stratification in Stage III Disease

The largest fraction of newly diagnosed patients are diagnosed with stage III colon cancer (29% of the total incident population.) Although the US Gastrointestinal (GI) Intergroup randomized clinical trials incorporating adjuvant chemotherapy for stage III colon cancer suggest a median overall 5-year survival of 63% to 65%,[1] it has become clear that patients with stage III disease do not constitute a single aggregate with homogeneous risk, but rather reflect subsets of patients with highly variable rates of survival. In recognition of the diversity of the stage III colon cancer population, the American Joint Committee on Cancer has revised the staging system defining stage III disease to include three different subsets: stages IIIA (T1–2N1M0), IIIB (T3–4N1M0) and IIIC (T any N2M0).[2]

Recently, Gill et al[3] published a model estimate of survival stratified by age, T stage, nodal status, and grade in an effort to define risk of recurrence for an individual patient for whom adjuvant chemotherapy is being considered after successful surgery (Table 1). Stratification showed striking differences in 5-year disease-free-survival (DFS) both when surgery alone was used and when patients received 5-fluorouracil (5-FU) plus leucovorin (LV) adjuvant therapy. For example, among the patients with the best prognosis were those with T1 to T2 disease, 1 to 4 positive lymph nodes, and a low-grade tumor; these patients had 5-year DFS of 62% with surgery alone and 75% with adjuvant treatment. At the other end of the spectrum are patients with a T4 high-grade tumor and more than five positive lymph nodes, who have projected a 5-year DFS of only 5% with surgery and 17% with adjuvant therapy.

It also has become increasingly apparent that overall survival (OS) correlates with the number of lymph nodes that have been sampled and reported for patients with lymph node-positive disease.[4] For example, at 96 months after sur-

Division of Hematology/Oncology, Feinburg School of Medicine, Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL.

Dr Benson has received research funding and has served as a consultant to Bristol-Myers Squibb, Genentech, Imclone, Pfizer, Roche, and Sanofi-Aventis.

Address reprint requests to Al B. Benson III, MD, FACP, Division of Hematology/Oncology, Feinburg School of Medicine, Robert H. Lurie Comprehensive Cancer Center, Northwestern University, 675 North St Clair St, Chicago, IL 60611.

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Table 1 Estimates of 5-Year Disease-Free Survival (%) With Surgery With or Without 5-Fluorouracil-Based Adjuvant Therapy According to Nodal and T Status and Disease Grade

Nodal status	T Stage	Low Grade		High Grade	
		S	+AT	S	+AT
0 Nodes	T3	73	77	65	70
	T4	60	66	51	57
1-4 Nodes	T1–T2	62	75	53	68
	T3	49	65	38	56
	T4	33	51	23	40
>5 Nodes	T1–T2	39	57	28	46
	T3	24	43	15	32
	T4	11	27	5	17

Abbreviations: AT, adjuvant therapy; S, surgery.
Adapted from Gill et al.[3]

gery, there is a significant difference in survival for those patients who have more than 40 lymph nodes resected compared with those with 11 to 40 lymph nodes or 1 to 10 lymph nodes resected (respective survival of 90% *v* 64% *v* 56%).

It can thus be appreciated that a risk-stratified approach is of considerable importance to providing more accurate interpretation of clinical trial results. In the past, clinical trials have included relatively nonspecific stratification factors (ie, including age and performance status) that now appear inadequate to define the subsets of patients who are at greatest risk for recurrence. Given the number of patients required, it would be very difficult to design individual trials for the different subsets of stage III patients; however, at a minimum, stratification factors should include T status, number of positive nodes and number of nodes reported, and grade of tumor.

The ability to predict the potential benefit of therapy for an individual patient based on risk assessment, including tumor biological characteristics, is an important future goal. A number of investigators have attempted to define both prognostic and predictive markers based on retrospective analysis of tumor samples linked to randomized clinical trial outcome data. For example, the Eastern Cooperative Oncology Group collected paraffin-embedded tumor specimens from a subset of Eastern Cooperative Oncology Group patients who participated in two GI Intergroup, randomized, phase III trials from which mature outcome data were available.[1,5-7] The patients had received various schedules and combinations of 5-FU, LV, and levamisole. Laboratory investigations included an assessment of loss of heterozygosity on chromosome 18 (18q LOH) and the presence of microsatellite instability with or without mutated transforming growth factor-β1 receptor type II (TGF-β1 RII) (Fig 1). Patients who retained 18q alleles or who had microsatellite instability-positive tumors, particularly with mutated TGF-β1 RII, had a 5-year OS of approximately 75% compared with approximately 50% among those patients with loss of 18q alleles or without mutated TGF-β1 RII. As previously noted, the GI Intergroup data suggest a 5-year OS for the composite stage III population of 63% to 65%.[1] All current cooperative group adjuvant clinical trials include collection of patient tumor specimens. The trials incorporate prospective hypothesis-driven laboratory correlates in an extensive effort to define reproducible prognostic and predictive markers. It is the hope that risk-benefit ratios based on tumor biological characteristics will emerge that will help to better define individual patient treatment strategies.

Recent Advances in Adjuvant Chemotherapy

Since 2000, a number of randomized clinical trials addressing the efficacy of infusional 5-FU, oral chemotherapy, and combination therapy with both irinotecan and oxaliplatin have yielded mature results. A GI Intergroup trial of Poplin et al[8] compared a bolus Mayo Clinic regimen of 5-FU/LV plus levamisole with continuous infusion 5-FU in three 8-week cycles plus levamisole, and showed the equivalence of these treatments. Similarly, a recently reported trial by Saini et al[9]

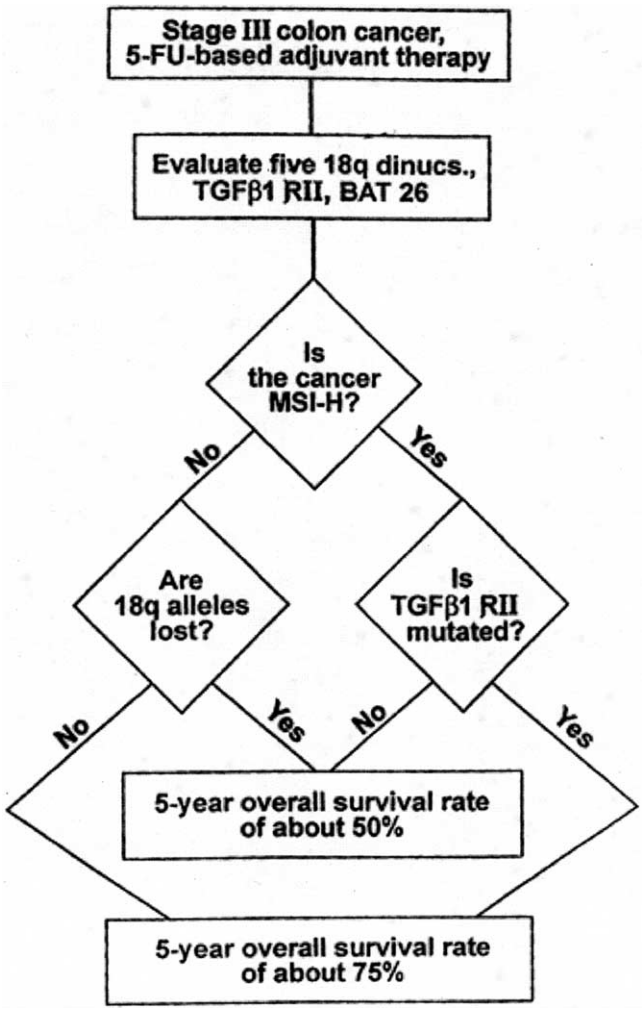

Figure 1 Effect of 18q LOH and presence of microsatellite instability on survival in patients receiving 5-FU–based adjuvant therapy. 18q LOH, loss of heterozygosity on chromosome 18; 5-FU, 5-fluorouracil; MSI-H, microsatellite instability–high; BAT 26, Big A-Tract 26 adenine residues; dinucs, dinucleotides; MSI, microsatellite instability; TGFβ1, transforming growth factor-β1 receptor type II.

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