Stage II Colorectal Cancer: To Treat or not to Treat

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INTRODUCTION

Colorectal cancer (CRC) accounts for 10%–15% of all cancers and is the leading cause of cancer deaths in the Western world. Up to 40%–50% of patients who undergo potentially curative surgery alone ultimately relapse and die of metastatic disease [1]. The most important prognostic indicator for survival in colon cancer is tumor stage, which is determined by the depth of penetration through the bowel wall and the number of lymph nodes involved.

Over the last 15 years, the development of adjuvant chemotherapy given after surgical removal of tumors for patients with stage II and stage III disease has been used to reduce the risk of recurrence of cancer that may result from remaining tumor cells not detectable after surgery. Many thousands of patients with CRC have been included in clinical trials to assess the potential benefit of various combinations of chemotherapeutic agents.

Since the National Institutes of Health 1990 consensus conference, the administration of adjuvant 5-fluorouracil (FU)–based therapy for all medical patients with stage III colorectal cancer has become standard of care and has resulted in a 30%–40% decrease in relapse and mortality rates versus treatment with surgery alone [2]. At the time, the panel did not recommend adjuvant therapy for stage II CRC patients outside the realm of clinical trials, as the data at that time did not support adjuvant therapy for stage II disease. However, one of the problems in the analysis of stage II disease has been the requirement for very large numbers of patients due to the overall favorable prognosis for this subgroup of patients. In adjuvant CRC studies, most clinical trials have included patients with both stage II and stage III disease, and most of those trials have been insufficiently powered to detect any treatment benefit in stage II patients.

In stage II CRC, there is tumor penetration through the bowel wall involving the serosa; however, there is no involvement of regional lymph nodes or distant metastases. While the overall survival in this subgroup of patients is approximately 70%–80% 5 years after surgery, in high-risk stage II disease, the clinical outcome is similar to that of patients with stage III disease. Currently, these high-risk patients are identified by tumors that not only penetrate the bowel wall but also show evidence of adhesion to or invasion of surrounding structures, free perforation, obstruction, or aneuploidy. More importantly, recent data, using molecular markers such as loss of heterozygosity (LOH) of 18q or the presence of microsatellite stable tumors, have helped to identify a subgroup of patients with both stage II and stage III CRC who may have much worse prognoses and in whom the administration of chemotherapy may be beneficial.

EVIDENCE FOR AND AGAINST TREATMENT

In an analysis of four trials, the National Surgical Adjuvant Breast and Bowel Project (NSABP) showed that the relative benefits were largely the same for patients with stage II and stage III tumors for both disease-free survival and overall survival [3]. Each study included node-negative and
node-positive patients, with the node-negative subset accounting for approximately 40% of accrual. These data were supported by a meta-analysis from the Mayo Clinic that looked at data from 3,341 patients with both node-negative and node-positive colon cancer [4]. The results from that study demonstrated benefit from adjuvant therapy in stage II CRC, though to a lower extent than that seen in stage III disease. In addition, a recently published meta-analysis conducted by the Japanese Cancer Society demonstrated that oral fluoropyrimidines improved disease-free survival and overall survival for patients with stage I, stage II, and stage III tumors, with a greater relative effect in stage I or stage II [5]. A report from the Quick and Simple and Reliable (QUASAR) study compared adjuvant 5-FU–based therapy with observation in 3,238 CRC patients (91% Dukes’ B) from 150 centers in 17 countries. After a median follow-up of 4.2 years, they observed a significant decrease in disease recurrence and a 1%–5% improvement in survival in the 5-FU–treated cohort [6]. Therefore, overall, these studies suggest that patients with node-negative CRC may have a similar incremental benefit as patients with stage III disease.

In contrast, the International Multi-centre Pooled Analysis of Colon Cancer Trials (IMPACT) B2 study, which combined data from patients in five separate trials, did not show any statistically significant benefit of 5-FU/leucovorin combinations over surgery alone in stage II patients [7]. Those studies enrolled 1,025 patients who had stage II node-negative colon cancer into four Canadian/European and several North Central Cancer Center Treatment Group (NCCCTG) trials. The overall survival rates at 5 years were 80% for the control group and 82% for the treatment group, suggesting that for every 100 individuals with node-negative disease, adjuvant 5-FU therapy only benefited two of them.

Recently, an American Society of Clinical Oncology panel reviewed the available literature-based evidence regarding adjuvant therapy in stage II patients [8]. The results of that review showed that although there was evidence of improvement in disease-free survival with adjuvant therapy, there was no significant improvement in overall survival in stage II CRC patients. The authors concluded that it was reasonable to recommend against the use of such therapy and equally reasonable to recommend in favor of its use to well-informed patients. Of note, that review did not take into account the impact of newer combinations, such as those studied in the Multicenter International Study of Oxaliplatin/5-FU/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) study [9].

Several recent clinical studies have explored newer chemotherapeutic agents in stage II patients. The MOSAIC trial, which randomized patients to receive either infusional 5-FU or infusional 5-FU with oxaliplatin (Eloxatin®; Sanofi-Synthelabo Inc., New York, NY, http://www.sanoﬁ-synthelabo.us) (FOLFOX4) demonstrated a significant improvement in 3-year disease free survival for more than 1,100 patients who were treated with FOLFOX [9]. Forty percent of those patients were node negative and (this cohort treated with FOLFOX) demonstrated an improvement in disease-free survival that approached statistical significance and a hazard ratio of 18%, similar to that in the stage III group. However, the value of any benefit from newer combinations must be weighed against the inconvenience and potential side effects of 5-FU/oxaliplatin treatment.

There are several major reasons why the thorny issue of adjuvant 5-FU-based chemotherapy for patients with stage II colon cancer remains a heated topic of debate and one of considerable controversy. Buyse and Piedbois attributed the lack of any demonstrable survival benefit primarily to the insufficient number of patients in trials to adequately address this particular issue [10]. This particularly relates to the fact that these patients have relatively good prognoses as well as a high frequency of noncancer–related deaths. It has been suggested that a study involving over 8,000 patients would be needed to detect a survival difference of 2% between a treatment and control arm in this population [10]. However, with the recent advent of more active agents in CRC, a study comparing a 5-FU/oxaliplatin or 5-FU/irinotecan (Camptosar®; Pfizer Pharmaceuticals, New York, NY, http://www.pfizer.com) combination with no therapy may require a much smaller number of patients.

**MOLECULAR MARKERS**

More recently, there has been an attempt to identify novel panels of molecular and biochemical markers that may be used to more precisely define prognosis and predict benefit of adjuvant treatment in colorectal cancer. Several retrospective studies have suggested that a number of markers may now define patients with a higher risk of relapse with both stage II and stage III disease. These markers include studies examining 18q LOH, microsatellite instability, and thymidylate synthase [11–14]. The most promising candidate markers at present are allelic loss of chromosome 18q and microsatellite instability. Several studies have demonstrated that patients who have lost 18q have a worse 5-year survival rate than patients who retain both alleles. In addition, retention of both 18q alleles had a more favorable outcome after adjuvant 5-FU-based chemotherapy in stage II disease [11, 12]. In a retrospective study of 570 patients enrolled in three trials of adjuvant 5-FU-based therapy, the 5-year survival rate was significantly better in those patients whose tumors exhibited high-frequency microsatellite instability [13]. The role of these predictive markers is currently
being tested in stage II patients in a Gastrointestinal Intergroup study conducted by the Eastern Cooperative Oncology Group (E5202) that will address their potential as predictors of chemotherapy response.

Finally, Wang and colleagues recently used microarray technology and gene-expression profiling to identify markers of risk of relapse in stage II patients [15]. They identified a 23-gene marker set that they validated in 36 patients with stage II disease. Those patients with stage II disease who had increased expression of these genes had a 13-fold higher risk of relapse than those who did not have overexpression of this gene set. That study highlights the potential of gene-expression profiling to identify subsets of patients with stage II disease who may benefit most from chemotherapy.

CONCLUSION
In conclusion, randomized controlled trials and meta-analyses have uniformly failed to definitively detect a survival benefit for adjuvant chemotherapy in stage II CRC. These trials have included insufficient numbers of patients with stage II disease to ultimately determine whether adjuvant chemotherapy in this population is truly beneficial. Nonetheless, there remains no clinical or biological reason to believe that the clinical behavior of stage II tumors should be different from that of stage III tumors. Therefore, clinical trials in stage II CRC must incorporate better risk stratification using molecular markers and an adequate number of patients to define the relative disease-free and overall survival benefits from chemotherapy. Patients with stage II disease must be allowed access to clinical trials that once and for all answer this important question.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST
The author indicated no potential conflicts of interest.

REFERENCES