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Adjuvant Therapy Trials

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Abstract

In 2015, ramucirumab and TAS-102 became the 10th and 11th drugs approved by the Food and Drug administration for the treatment of patients with colorectal cancer, not counting leucovorin, and yet only 3 agents, 5-fluorouracil, capecitabine, and oxaliplatin, have proven benefit in adjuvant treatment. In fact, there have been no additions (and 1 subtraction levamisole) to our arsenal of therapies for patients with stages II and III colon cancer for more man a decade. How did we get here? Are we stuck? And how do we move forward?

Keywords

Adjuvant chemotherapy; clinical trial review; colon cancer

CURRENT STANDARDS OF CARE

It is easy to forget that adjuvant treatment for colon cancer was not standard until 1989 when the results of a randomized trial comparing observation to levamisole, with or without 5-fluorouracil (5-FU), prompted the National Cancer Institute to circulate a clinical update summarizing the data. The 5-FU/levamisole arm in that landmark study improved 5-year overall survival (OS) in Dukes' C patients from 37% to 49%.[1] While there is much to criticize about that trial, including the absence of a 5-FU alone arm and the ultimate withdrawal of levamisole from the marketplace because of its association with a demyelinating syndrome, this trial established the baseline upon which subsequent research would build.

Since then, fiberoptic and imaging technology and surgical techniques have improved our ability to diagnose, stage, and resect colon cancer, and many drugs have been shown to be effective in the treatment of metastatic disease. However, despite dozens of trials since that time, the only major advance in adjuvant therapy has been an additional 5% increase in disease-free survival (DFS) from the addition of oxaliplatin to 5-FU/leucovorin (LV).

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Resected Stage III Colon Cancer

The current standard of care for adjuvant treatment of resected stage III colon cancer is combination chemotherapy with 5-FU/LV and oxaliplatin (FOLFOX).[2] There are 3 large clinical trials that inform this standard, each with differences in the administration schedule of intravenous 5-FU or the substitution of an oral fluoropyrimidine for 5-FU.

The first trial to show a survival advantage of an oxaliplatin-containing regimen was MOSAIC, an international trial of 2246 patients with stage II or III colon cancer. This trial compared infusional 5-FU/LV versus 5-FU/LV plus oxaliplatin. At first analysis, improvement in 5-year DFS was seen with the addition of oxaliplatin (hazard ratio [HR], 0.8; 95% confidence interval [CI], 0.68–0.93).[3] After 6 years of follow-up, the addition of oxaliplatin translated into a significant OS benefit (72.9% vs. 68.7%; HR, 0.8; 95% CL 0.65–0.97). Subset analyses of patients with stage II cancer and of elderly patients[4] showed no significant DFS or OS advantage in either group.

The parallel trial, NSABP C-07, was a US trial of 2407 patients with resected stage II or III colon cancer that also compared 5-FU/LV with or without oxaliplatin. The primary endpoint was 4-year DFS, which was 73.2% with the addition of oxaliplatin, compared with 67% for 5-FU/LV alone.[5] A subset analysis of stage II patients showed neither an OS (HR, 1.04; 95% CI, 0.72–1.50) or a DFS benefit (HR, 0.94; 95% CI 0.70–1.26) in this group.

At the same time that the addition of oxaliplatin to 5-FU/LV was being studied, others were evaluating the substitution of the oral fluoropyrimidine capecitabine for infusional 5-FU/LV.[6] Investigators found at least noninferior DFS and OS, with comparable but distinct toxicity profiles (e.g., a slight increase in hand-foot syndrome with capecitabine and more neutropenia with 5-FU/LV). Based on these results, the XELOXA trial randomized 1886 patients with stage III resected colon cancer to capecitabine plus oxaliplatin (XELOX) versus 5-FU/LV.[7] Final analysis revealed a 7-year OS of 73% in the XELOX arm compared with 67% with 5-FU/LV (HR, 0.83; 95% CI 0.7–0.99).[8]

While the 3 different oxaliplatin-containing regimens represented in these trials are all considered acceptable according to current National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines,[2] they have never been compared head to head. In practice, the most commonly used regimen is mFOLFOX6; however, it is worth noting that this regimen was not actually used in any of the aforementioned trials. The mFOLFOX6 regimen differs from the FOLFOX4 regimen used by MOSAIC by the deletion of the 5-FU bolus on day 2. Recognizing the limits of cross-study comparisons, the FLOX regimen of NSABP-C07 appears to be associated with more toxicities than the others[9] despite the use of less total oxaliplatin, specifically febrile neutropenia and gastrointestinal symptoms.

Resected Stage II Colon Cancer

With respect to patients with stage II disease, the role of adjuvant chemotherapy is less clear. The average-risk stage II patient has an estimated 5-year OS of 75% to 80% with surgery alone, which has not been shown to significantly improve with adjuvant chemotherapy.[10] However, a trend toward improved DFS was reported in patients with stage II disease who received oxaliplatin from the MOSAIC subgroup analysis,[3] and many attempts have been

made at identifying a subset of stage II patients who benefit from the delivery of adjuvant chemomerapy. There are several factors that are known to be associated with a poor prognosis, defining “high-risk” stage II disease. These established factors include T4 disease characterized by invasion into the visceral peritoneum,[11] decreased number of resected lymph nodes,[12] poorly differentiated histology,[11] lymphovascular invasion,[13] and obstruction or perforation evident at the time of surgery.[10] Per NCCN guidelines, all of these high-risk features are indications to consider adjuvant chemotherapy; however, none have been proven to predict for benefit from adjuvant chemotherapy administration. Given the lack of clarity regarding which high-risk stage II patients are likely to benefit from adjuvant chemotherapy, ongoing efforts are aimed at trying to identify predictive molecular markers. To date, the most convincing work has been in showing that defects in the mismatch repair system predict a lack of benefit to adjuvant fluoropyrimidine-based chemotherapy.[14] Although other molecular makers such as 18q loss of heterozygosity, BRAF mutation status, and gene expression arrays have been used as further prognostic markers, none have been shown to be predictive of adjuvant therapy benefit.

Elderly Patients

There is currently no clear consensus regarding the role for adjuvant treatment of resected stage III colon cancer in elderly patients, and current NCCN guidelines caution that a benefit of the addition to oxaliplatin to 5-FU/LV has not been proven for older patients.[2] The lack of clarity is largely due to the underrepresentation of elderly patients in clinical trials. While the median age at diagnosis of colon cancer is 72 years, the median age ofcolon cancer clinical trial patient is near 60 years.[5,7,15] The results of subset analyses of older patients from the MOSAIC, NSABP-C07, and XELOXA trials have been conflicting, with some not showing a benefit for the addition of oxaliplatin to 5-FU/LV in patients 70 years or older. None of these trials were powered sufficiently for a conclusive subset analysis.[4,7,16] There are, however, strong data substantiating mat the benefit of adjuvant 5-FU in stage in colon cancer is conserved in patients 70 years or older.[17] Despite this, patients 75 years or older are less likely to receive not only oxaliplatin containing adjuvant chemotherapy, but also any adjuvant therapy at all.[18]

LESSONS LEARNED FROM NEGATIVE TRIALS

Since the publication of MOSAIC in 2004, there have been more negative than positive trials evaluating additional therapies in the adjuvant setting (Table 1). Nearly all of these negative trials have attempted to move regimens mat are effective in treatment of metastatic disease into the adjuvant space. CALGB 89803 was initiated prior to oxaliplatin-containing regimens becoming standard of care and evaluated 5-FU/LV with and without the addition of irinotecan in patients with stage III disease.[19] It showed no DFS or OS benefit from the addition of irinotecan and significantly increased toxicity. The lack of benefit from irinotecan was confirmed by the ACCORD02[20] and PETACC-3[21] trials, firmly removing this agent from the adjuvant setting. Although CALGB 89803 was ultimately a negative trial, much of what we have learned about the impact of lifestyle and other modifiable risk factors in stage III colon cancer survivors came from correlative studies conducted among CALGB 89803 participants.[22]

In the wave of excitement following the approvals of bevacizumab, cetuximab, and pantitumumab for the treatment of metastatic colorectal cancer, several trials sought to evaluate potential additive benefits of targeting either vascular endothelial growth factor or the epidermal growth factor receptor pathway in the adjuvant setting, with FOLFOX as a chemotherapy backbone. NSABP-C08 evaluated 12 cycles of mFOLFOX6 with and without 12 months of the vascular endomelial growth factor inhibitor bevacizumab in patients with stages II and III colon cancer.[23] This trial demonstrated no DFS or OS benefit from the addition of bevacizumab and also identified an increase in toxicities attributable to bevacizumab, including hypertension, protein-uria, and impaired wound healing. The AVANT trial compared FOLFOX4 versus FOLFOX4 plus bevacizumab versus XELOX plus bevacizumab and similarly found no survival benefit but increased toxicity with bevacizumab use.[24] Based on these results, the ECOG 5202 study of mFOLFOX6 with or without bevacizumab in high-risk stage II patients was terminated early. With respect to the role of epidermal growth factor receptor inhibitors in adjuvant therapy, FOLFOX with and without cetuximab in patients with wild-type KRAS stage III disease was evaluated in the NCCTG (North Central Cancer Treatment Group) N0147 trial.[25] Similar to the bevacizumab studies, there was no benefit from the addition of cetuximab.

FUTURE DIRECTIONS

Although attempts to further improve colon cancer survival through development of new adjuvant chemotherapy regimens have been fruitless, both determining the optimal delivery of current adjuvant regimens and selection of patients likely to benefit from adjuvant therapy offer opportunities for improvement. In an attempt to decrease toxicities associated with adjuvant treatment, the currently pending International Duration Evaluation of Adjuvant Chemotherapy Colon Cancer Prospective Pooled Analysis will pool data from more than 11,500 patients in 6 randomized phase III trials to compare the effectiveness of 6 versus 12 cycles of adjuvant FOLFOX in patients with stage III disease.[26] If 3 months of mFOLFOX6 is found to be noninferior to 6 months, future patients would potentially be spared 3 unnecessary months of chemomerapy, truncating adjuvant therapy prior to the timeframe at which cumulative oxaliplatin-induced neuropathy typically becomes problematic. Additional opportunities to improve upon mFOLFOX6 as the current standard include the evaluation of chemoprevention agents, such as nonsteroidal anti inflammatory drugs, cyclooxygenase 2 inhibitors, and vitamin D, as adjuncts to chemotherapy.

Finally, improved patient selection for adjuvant chemotherapy, particularly among elderly patients and those with stage II disease, remains a priority area for ongoing investigations. A promising example of work in the arena utilizing biomarkers to predict for benefit from adjuvant chemotherapy is a recent study looking at the predictive value of CDX2 expression by immunohistochemistry. This retrospective study identified absent CDX2 expression as a marker of both poor prognosis and increased benefit from adjuvant chemomerapy in stages II and III colon cancer patients.[27] Although a confirmatory randomized trial is needed, personalization of treatment decisions offers great opportunity for selecting the right therapies for our patients in the future.

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TABLE 1

Negative Phase III Trials of Adjuvant Chemotherapy in Stage III Colon Cancer 2009–2012

Trial	Reference	Patients	Design	Summary
CALGB 89803	Saltz et al.[19]	Stage III (n = 1264)	6 mo FOLFIRI vs. 5-FU/LV	5-y OS 68% in FOLFIRI vs. 71% in 5-FU/LV arm; 5-yr DFS 59% in FOLFIRI vs. 61% in 5-FU/LV arm
PETACC-3	van Cutsem et al.[21]	Stage II (n = 1184) and stage III (n = 2094)	6 mo FOLFIRI vs. 5-FU/LV	For stage III 5-y OS 73% in FOLFIRI vs. 71% in 5-FU/LV; 5-y DFS 57% in FOLFIRI vs. 54% in 5-FU/LV (HR, 0.9, $P = 0.106$)
ACCORD02	Ychou et al.[20]	Stage III (n = 400)	6 mo FOLFIRI vs. 5-FU/LV	5-y OS 61% in FOLFIRI vs. 67% in 5-FU/LV; 3-y DFS 51% in FOLFIRI vs. 60% in 5-FU/LV
NSABP-C08	Allegra et al.[23]	Stage II (n = 666) and stage III (n = 2006)	6 mo of mFOLFOX6 +/− 12 mo of bevacizumab	3-y DFS 77.4% vs. 75.5% for experimental vs. control arm (HR, 0.89; $P = 0.15$)
AVANT	de Gramont et al.[24]	High-risk stage II (n = 583) and stage III (n = 2867)	6 mo of FOLFOX4 +/− 12 mo bevacizumab, and 6 mo XELOX +/− 12 mo bevacizumab	For stage III patients DFS vs. FOLFOX4 for FOLFOX4 + bevacizumab HR 1.17 (95% Cl, 0.98–1.39), for XELOX + bevacizumab HR 1.07 (95% Cl, 0.9–1.28)
ECOG 5202	—	Stage II high vs. low risk	For high risk mFOLFOX6 +/− bevacizumab; observation for low risk	Study terminated
NCCTG N0147	Alberts et al.[25]	Stage III wild-type KRAS (n = 1760)	6 mo of mFOLFOX6 +/− cetuximab	3-y DFS favored mFOLFOX6 alone HR 1.18 (95% Cl, 0.92–1.52)