Combination therapy in high-risk stage II or stage III colon cancer: current practice and future prospects

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Abstract: Colon cancer represents the second leading cause of cancer-related deaths. For patients who have undergone curative surgery, adjuvant therapy can reduce the risk of recurrence and death from relapsed or metastatic disease. Postoperative chemotherapy with a 5-fluorouracil-based regimen combined with oxaliplatin is the current standard of care for stage III patients. However, there is still controversy in stage II disease about the real impact of adjuvant monotherapy or combined therapy on survival. Better identification of a subgroup of patients with a higher risk of recurrence can select patients who might benefit from adjuvant therapy. For the elderly population, there is a well-established role for postoperative therapy, although the most appropriate regimen remains to be defined. Targeted agents for combined adjuvant therapy in stage II and III colon cancer is a promising area, but to date, there is no evidence supporting its use in this setting. Results from large prospective trials with targeted therapy have been disappointing and new drugs and strategies are needed to define the role of these types of agents in the adjuvant scenario of colon cancer.

Keywords: adjuvant chemotherapy, colon cancer, combined therapy, high-risk stage II, stage III

Introduction

At least one million new cases of colon cancer are diagnosed every year worldwide. It represents one of the most common neoplasms and the second leading cause of death for cancer, accounting for 9% of total cancer fatalities [Jemal *et al.* 2009]. Approximately 75–80% of newly diagnosed patients have localized or regional tumors and surgery remains the unique curative treatment for these patients. However, up to 50% of patients will relapse after surgical resection and ultimately die of metastatic disease [De Dosso *et al.* 2008; Kopetz *et al.* 2008; Marshall *et al.* 2007; de Gramont *et al.* 2005]. The objective of adjuvant postoperative chemotherapy is to reduce the risk of recurrence and improve a patient's outcome by eliminating any occult, viable tumor cells that may have remained after surgery.

The prognosis of colon cancer is directly related to the risk of recurrence, which is better predicted by pathologic staging. Stage I colon cancer patients have a 5-year survival rate of approximately 93% and therefore these patients do not benefit from

adjuvant treatment. Patients with stage II disease represent about 25% of cases and have a 5-year overall survival (OS) ranging from 84.7% for T3N0 (IIa) to 72.2% for T4N0 (IIb). Stage III patients are stratified into three subgroups with different 5-year OS: 83.4% for IIIa (T1–2N1), 64.1% for IIIb (T3–4N1), and 44.3% for IIIC (T0–4N2) [O'Connell *et al.* 2004]. Of note, survival from stage IIb colon cancer is statistically inferior to stage IIIa tumors, whether this is due to widespread use of adjuvant therapy in stage III disease remains unclear.

Despite the general agreement on postoperative chemotherapy for stage III colon cancer, there is still debate on this approach for stage II tumors. Recently, several high-risk features have been identified to guide therapeutic decision on adjuvant therapy in this setting and probably high-risk stage II patients may benefit from treatment.

Based on available current data, combination therapy is the standard treatment for stage III colon cancer. However, there is still controversy

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about whether or not combined therapy can improve outcome in high-risk stage II patients and also in the elderly population. This review addresses the current debate over the use of combined adjuvant chemotherapy in high-risk stage II and stage III colon cancer.

Historical perspective

The first solid evidence of benefit from adjuvant chemotherapy for colon cancer emerged in 1990. The Intergroup 0035 trial of 5-fluorouracil (5-FU) plus levamisole (lev) compared with lev alone or observation demonstrated a 41% relative reduction in recurrence rate and a significant survival advantage for patients on the 5-FU/lev arm, with a median 5-year OS of 60% for adjuvant chemotherapy versus 46.7% and 49% for observation and lev alone, respectively ($p = 0.0007$) [Moertel *et al.* 1995, 1990].

After these results, successive trials have demonstrated the superiority of 5-FU/leucovorin (LV)

compared with 5-FU/lev. The National Surgical Adjuvant Breast and Bowel Project (NSABP) C-04 trial showed a superiority of 5-FU/LV for both OS and disease-free survival (DFS), with a 13% and 10% relative risk reduction for DFS and OS, respectively. For stage II disease there was a reduction in recurrence rate of 22% suggesting a potential role of adjuvant 5-FU/LV in this setting. These results supported the routine use of adjuvant 5-FU/LV as adjuvant treatment in stage III patients and a potential role of this approach for stage II patients [Wolmark *et al.* 1999].

Another important trial was the Intergroup 0089 trial, which compared the efficacy of 5-FU/LV and 5-FU/lev and also compared two regimens of 5FU/LV, the 5-FU/high-dose LV (Roswell Park) and the 5-FU/low-dose LV regimen (Mayo Clinic) (Table 1). There were four treatment arms in this trial: 5-FU/lev (12-month protocol), 5-FU/high-dose LV (Roswell Park, 7 months), 5-FU/low-dose LV (Mayo, 6 months), and

Table 1. Adjuvant chemotherapy protocols used in clinical trials.

Protocol	Drugs/doses/schedule	References
5-FU/LV Mayo Clinic	LV 20 mg/m ² /day iv for 5 days every 4 weeks, for six cycles 5-FU 425 mg/m ² /day iv for 5 days every 4 weeks, for six cycles	[Haller <i>et al.</i> 2005]
5-FU/LV Roswell Park	LV 500 mg/m ² iv, 6 weekly courses every 8 weeks, for three to four cycles 5-FU 500 mg/m ² iv, 6 weekly courses every 8 weeks, for three to four cycles	[Haller <i>et al.</i> 2005]
QUASAR	LV 25 mg/day iv for 5 days every 4 weeks, for six cycles 5-FU 370 mg/m ² /day iv for 5 days every 4 weeks, for six cycles	[Gray <i>et al.</i> 2007]
FLOX	LV 500 mg/m ² iv, 6 weekly courses every 8 weeks, for three cycles 5-FU 500 mg/m ² iv, 6 weekly courses every 8 weeks, for three cycles	[Kuebler <i>et al.</i> 2007]
5-FU/LV2	Oxaliplatin 85 mg/m ² iv on days 1, 15 and 29 of each cycle LV 200 mg/m ² iv every 2 weeks, for six cycles 5-FU 400 mg/m ² iv bolus followed by 600 mg/m ² iv 22 h infusion for 2 consecutive days every 2 weeks, for six cycles	[André <i>et al.</i> 2004]
FOLFOX4	LV 200 mg/m ² iv every 2 weeks, for six cycles 5-FU 400 mg/m ² iv bolus followed by 600 mg/m ² iv 22 h infusion for 2 consecutive days every 2 weeks, for six cycles	[André <i>et al.</i> 2004]
mFOLFOX6	Oxaliplatin 85 mg/m ² every 2 weeks, for six cycles LV 400 mg/m ² iv every 2 weeks, for six cycles 5-FU 400 mg/m ² iv bolus followed by 2400 mg/m ² iv 46 h infusion every 2 weeks, for six cycles	[Wolmark <i>et al.</i> 2009]
XELOX	Oxaliplatin 85 mg/m ² every 2 weeks, for six cycles Capecitabine 1000 mg/m ² twice daily for 14 days every 3 weeks, for eight cycles Oxaliplatin 130 mg/m ² every 3 weeks, for eight cycles	[Schmoll <i>et al.</i> 2007]
5-FU, 5-fluorouracil; iv, intravenously; LV, leucovorin.		

5-FU/LV/lev (6 months). After a 10-year follow up, results for both 5-year DFS and OS were similar in all treatment arms [Haller *et al.* 2005].

At that time, bolus 5-FU/LV (the Roswell Park or Mayo Clinic regimen) was considered the standard adjuvant therapy for stage III colon cancer. Since then, the availability of active chemotherapy agents, outcome improvement with combination chemotherapy, and redefinition of clinical benefit for high-risk stage II colon cancer and for the elderly population have modified the understanding and management of adjuvant therapy for colon cancer.

Adjuvant therapy for stage III colon cancer

Monotherapy regimens

As previously mentioned, several studies have established adjuvant therapy with 5FU/LV as the standard for patients with stage III colon cancer [Haller *et al.* 2005; Wolmark *et al.* 1999]. Although there was no established standard dosing schedule for 5-FU/LV or defined treatment duration, important concepts could be learned from available trials. It has been demonstrated that 6 months of 5-FU/LV treatment was equivalent to 12 months of 5-FU/lev or 5-FU/LV/lev [Haller *et al.* 2005; O'Connell *et al.* 1998], low-dose LV was as effective as high-dose LV in combination with bolus 5-FU [QUASAR Collaborative Group, 2000], and regimens of 5-FU administered by continuous infusion or those combining bolus and infusional 5-FU are better tolerated and have similar efficacy compared with bolus 5-FU regimens [Poplin *et al.* 2005; André *et al.* 2003].

Oral fluoropyrimidines were also tested as monotherapy in the adjuvant setting. In a large randomized phase III trial, capecitabine was compared with bolus 5-FU/LV (Mayo regimen) for stage III colon cancer. The results demonstrated superiority in relapse-free survival in the capecitabine arm (hazard ratio [HR], 0.86; $p=0.04$) and also a trend toward superior DFS (HR, 0.87; $p=0.052$) and OS (HR, 0.84; $p=0.07$) for capecitabine *versus* bolus 5-FU/LV [Twelves *et al.* 2005]. In the NSABP C-06 trial, which evaluated tegafur-uracil (UFT) in the adjuvant treatment for stage II and III colon cancer, UFT/folinic acid (FA) achieved similar DFS and OS as compared with bolus 5-FU/FA [Lembersky *et al.* 2006].

Combination therapy

Oxaliplatin and irinotecan are known active drugs for metastatic colorectal cancer and both were tested as combined therapy with 5-FU/LV in the adjuvant treatment of colon cancer.

Oxaliplatin. Benefit for combination therapy with oxaliplatin in the adjuvant setting was first demonstrated in the MOSAIC trial [André *et al.* 2004]. In this study, 2246 stage II (40%) and stage III (60%) patients were randomized to receive 5-FU/LV infusion regimen alone or plus oxaliplatin 85 mg/m² (FOLFOX4 regimen). Overall, the 5-year DFS was significantly higher in the FOLFOX arm than in the 5-FU/LV monotherapy group, with 73.3% *versus* 67.4% ($p=0.003$, HR, 0.80). For stage III patients, the 5-year DFS was 66.4% for FOLFOX4 and 58.9% for the 5-FU/LV arm, with a significant risk reduction of 22% (Figure 1). The advantage favoring the combined treatment regimen was observed in all subgroups of stage III colon cancer, with a reduction in risk of recurrence of 7% in patients with stage III N1 disease and 12% in patients with stage III N2 disease. The 6-year update of the MOSAIC trial demonstrated that the addition of oxaliplatin resulted in an OS advantage of 2.5% ($p=0.046$) and 4.2% ($p=0.023$) for the entire study population and stage III patients, respectively [André *et al.* 2009] (Figure 2). Together with DFS and OS benefit, the combined treatment arm had a higher incidence of grade 3/4 toxicities in the MOSAIC trial. The addition of oxaliplatin to 5-FU/LV was associated with an increase in neutropenia (41% *versus* 4.7%), febrile neutropenia (1.8% *versus* 0.2%), diarrhea (10.8% *versus* 6.7%), vomiting (5.9% *versus* 1.4%), allergy (3% *versus* 0.2%), and neuropathy (12.4% *versus* 0%), but no increase in mortality.

The second trial that demonstrated better outcomes with combined therapy was the NSABP C-07 [Kuebler *et al.* 2007]. In this trial 2407 patients with stage II (29%) or III colon cancer were randomized to three cycles of bolus weekly 5-FU/LV alone or with oxaliplatin (FLOX regimen). Four-year DFS significantly favored the oxaliplatin group (73.2% *versus* 67%), with a 20% risk reduction in recurrence rate ($p<0.004$). In a preliminary report from the 2008 American Society of Clinical Oncology (ASCO) meeting, there was a trend toward better OS in the FLOX arm (5-year survival 80% *versus* 78%, HR, 0.85) [Wolmark *et al.* 2008].

Figure 1. Disease-free survival for stage III colon cancer in landmark clinical trials of adjuvant therapy. BEV, bevacizumab; FOLFOX, 5-fluorouracil plus oxaliplatin; 5-FU, 5-fluorouracil; F/U, follow up; HR, hazard ratio; lev, levamisole; LV, leucovorin; yr, years. INT-0035 [Moertel *et al.* 1995]; NSABP C-04 [Wolmark *et al.* 1999]; X-ACT [Twelves *et al.* 2005]; MOSAIC [André *et al.* 2009]; NSABP C-08 [Wolmark *et al.* 2009].

Figure 2. Overall survival for stage III colon cancer in landmark clinical trials of adjuvant therapy. FOLFOX, 5-fluorouracil plus oxaliplatin; 5-FU, 5-fluorouracil; F/U, follow up; HR, hazard ratio; lev, levamisole; LV, leucovorin; yr, years. INT-0035 [Moertel *et al.* 1995]; NSABP C-04 [Wolmark *et al.* 1999]; X-ACT [Twelves *et al.* 2005]; MOSAIC [André *et al.* 2009].

Overall, the toxicity of FOLFOX4 was lower than the FLOX regimen, with the exception of grade 3 sensory neuropathy, possibly because of the lower cumulative dose of oxaliplatin used in NSABP C-07 as compared with the MOSAIC trial. Conversely, gastrointestinal toxicity was more frequent in the FLOX regimen, possibly due to the different administration schedule of 5-FU/LV in the NSABP C-07 (bolus 5-FU/LV) and MOSAIC trial (infusional 5-FU) (Table 1). For these reasons, there is a general agreement that FOLFOX should be the regimen of choice, although FLOX could be used in patients for whom ambulatory infusional therapy is not available.

The first efficacy results of a phase III trial of combination adjuvant therapy with capecitabine and oxaliplatin (XELOX trial) were recently presented [Haller *et al.* 2009; Schmoll *et al.* 2007]. In this trial, 1886 stage III colon cancer patients were randomized to receive either XELOX or bolus 5-FU/LV (Mayo Clinic or Roswell Park), and after a median follow up of 57 months, the XELOX arm had a superior DFS (68.4% *versus* 62.3%, HR, 0.80, $p=0.0045$), and also a manageable toxicity profile.

Irinotecan. Despite documented efficacy of irinotecan for the treatment of metastatic colon cancer, trials of adjuvant therapy using this drug have failed to demonstrate improvement in DFS and OS.

The first trial of irinotecan in the adjuvant setting was the CALGB 89803. In this trial, 1264 stage III patients were randomized to 5-FU/high-dose LV alone or with irinotecan (IFL regimen) and no DFS or OS benefit was demonstrated [Saltz *et al.* 2007]. Of note, there were significantly higher rates of toxicities and treatment-related mortality in the IFL group (2.8% *versus* 1%). Interestingly, a recent subgroup analysis of this trial showed an apparent benefit of adding irinotecan in the adjuvant therapy of patients with microsatellite instability [Bertagnolli *et al.* 2009].

Owing to a better toxicity profile than the IFL regimen in the metastatic scenario, the FOLFIRI regimen was evaluated for adjuvant treatment of colon cancer in two randomized trials [Van Cutsem *et al.* 2009; Ychou *et al.* 2009]. Both the PETACC-3 trial and ACCORD trial have also failed to demonstrate benefit from adding irinotecan to 5-FU/FL in the adjuvant

setting. Also, patients with microsatellite instability did not benefit from combined treatment with irinotecan in a recent subgroup analysis of the PETACC-3 trial [Tejpar *et al.* 2009].

Based on the above-mentioned results, adjuvant irinotecan-combined chemotherapy cannot be considered a standard approach for resected colon cancer patients. There is controversy about whether patients with microsatellite instability can benefit from combined treatment with irinotecan and this approach cannot be recommended until more conclusive data are presented.

Adjuvant therapy for stage II colon cancer

As previously discussed, combined adjuvant chemotherapy has been considered a standard approach for stage III colon cancer. Despite the fact that patients with stage II disease have been included in several adjuvant trials (Figures 2 and 3), the benefit of chemotherapy after resection in these patients has not been definitively established. Better identification of a subgroup of patients with a higher risk of recurrence can select patients who might benefit from adjuvant therapy.

Definition of high-risk stage II colon cancer

Stage II colon cancer patients are a heterogeneous population in terms of prognosis. These patients have a relatively good outcome after surgery, with an OS of 72–85% and the role of adjuvant chemotherapy in this setting is still controversial [Kopetz *et al.* 2008].

Therefore, a better stratification of patients based on high-risk features should select a subgroup of patients with a higher risk of recurrence that might benefit from adjuvant therapy. On the other hand, this stratification may spare low-risk patients from receiving cytotoxic chemotherapy.

The well-known prognostic histological features in stage II disease are T4 tumor, perforation or obstruction, poorly differentiated histology, lymphovascular invasion [Quah *et al.* 2008; O'Connell *et al.* 2004], fewer than 12 sampled lymph nodes [Chang *et al.* 2007; Le Voyer *et al.* 2003; Prandi *et al.* 2002], and a high preoperative carcinoembryonic antigen level [Takagawa *et al.* 2008]. These factors have an important negative impact on survival and these patients have a 5-year OS of about 60%, similar to that of stage III patients [Quah *et al.* 2008; O'Connell *et al.* 2004]. Therefore, adjuvant treatment is

Figure 3. Disease-free survival for stage II colon cancer in landmark clinical trials of adjuvant therapy. BEV, bevacizumab; FOLFOX, 5-fluorouracil plus oxaliplatin; 5-FU, 5-fluorouracil; F/U, follow-up; HR, hazard ratio; lev, levamisole; LV, leucovorin; yr, years. INT-0035 [Moertel *et al.* 1995]; NSABP C-04 [Wolmark *et al.* 1999]; QUASAR [Gray *et al.* 2007]; MOSAIC [André *et al.* 2009]; NSABP C-08 [Wolmark *et al.* 2009].

often recommended for patients with one or more of these features, although its efficacy in this high-risk group has never been prospectively validated.

In addition to the well-recognized clinical and pathologic high-risk characteristics, molecular markers can also provide prognostic information. Microsatellite instability (MSI) is a measure of DNA repair mechanisms, which when disrupted lead to replication errors in repetitive nucleotide regions (called microsatellites), and the high-frequency MSI (MSI-H) is associated with a better survival compared with MSI-stable (MSI-S) tumors [Gryfe *et al.* 2000]. Although there are conflicting results about the role of MSI in the outcome of patients treated with adjuvant chemotherapy, most studies support the concept that adjuvant therapy is less beneficial for MSI-H tumors [Sinicrope and Sargent, 2009; Kim *et al.* 2007; Lanza *et al.* 2006; Popat *et al.* 2005; Ribic *et al.* 2003].

Other important candidate molecular prognostic markers are those related to chromosomal instability, particularly the loss of heterozygosity of the long arm of chromosome 18 (18q LOH). This is highly prevalent in sporadic colon cancer but its

utility as a prognostic tool remains to be defined. There are other molecular factors increasingly being evaluated for predicting outcome in stage II colon cancer, but the isolated use of these markers to assess prognosis or select patients for adjuvant chemotherapy cannot yet be recommended, as stated previously [Locker *et al.* 2006]. The ongoing ECOG E5202 trial is evaluating the role of molecular markers to select patients for adjuvant therapy or observation and the results are waited to define better this controversial matter.

Recently, a quantitative multigene real-time polymerase chain reaction assay provided a validated colon cancer recurrence score that was an independent predictor of individualized recurrence risk for stage II colon cancer patients following surgery [Kerr *et al.* 2009], but its use in clinical practice has not yet been defined.

Monotherapy regimens

An early prospective trial of adjuvant therapy for colorectal cancer reported an important benefit of short-term 5-FU for stage II patients, with a 5-year DFS of 82% compared with 59% in patients who did not receive adjuvant treatment ($p < 0.02$) [Li and Ross, 1976]. However, these

dramatic results have never been reproduced by other trials.

Subgroup analyses from the initial NSABP trials failed to show a statistically significant improvement in the outcomes of stage II patients treated with adjuvant chemotherapy [Smith *et al.* 2004; Wolmark *et al.* 1999, 1993, 1990].

The first study to report data separately for stage II patients evaluated adjuvant treatment with 5-FU/lev *versus* observation [Laurie *et al.* 1989]. There was a trend towards improved DFS in the 5-FU/lev arm (59% *versus* 73%; $p=0.10$). However, there was no OS benefit with adjuvant chemotherapy in this small stage II trial.

The subsequent Intergroup 0035 trial evaluated the impact of 5-FU/lev in 1247 stage II and stage III patients. However, it was underpowered to demonstrate benefit in stage II patients, as only 318 of these patients were studied. In this study, patients receiving 5-FU/lev were part of a trend towards a reduced rate of recurrence (71% *versus* 79% for observation and 5-FU/lev, respectively, $p=0.10$), with similar OS in the final report [Moertel *et al.* 1995, 1990].

In the QUASAR trial, 3239 patients (2146 [66%] with stage II colon cancer) with no clear indication for adjuvant chemotherapy were randomized to treatment with 5-FU/LV or observation [Gray *et al.* 2007]. After a median follow up of 5.5 years, the relative risk of recurrence and death from any cause with chemotherapy *versus* observation alone was 0.82 ($p=0.008$) and 0.78 ($p=0.001$), respectively. The authors concluded that the absolute benefit from an 18% relative reduction in mortality in this trial would be 5.4% in patients with high-risk features and 3.6% in those without, which might both be considered sufficient to justify adjuvant chemotherapy in this patient group. However, the inclusion of rectal cancer patients, administration of four 5-FU-based regimens and the lack of a central pathologic review make these results questionable.

Meta-analyses. Several meta-analyses had been published evaluating the role of adjuvant therapy for colon cancer, including stage II patients, with conflicting results.

The IMPACT B2 study evaluated five trials that had individual patient data for modified Duke's

B2 (T3-4N0) patients [IMPACT B2, 1999]. A total of 998 patients randomized to treatment with 5-FU/LV or observation were analyzed after a 5.8-year follow-up period. The 5-year OS rate was 82% on the 5-FU/LV arm *versus* 80% with observation alone (nonsignificant) and the HR at 5 years was 0.83 (90% confidence interval [CI], 0.72–1.07) for DFS and 0.86 (90% CI, 0.68–1.07) for OS.

A second study evaluated the benefit of adjuvant treatment in the NSABP C-01–C-04 trials [Mamounas *et al.* 1999]. In this analysis there was a 30% relative reduction in mortality for stage II patients ($p<0.05$), favoring the more effective treatment arms, with a corresponding decrease in risk of recurrence. Of note, the benefit in mortality occurred irrespective of the presence or absence of adverse prognostic factors and also this survival advantage was similar for stage II and III colon cancer.

On a pooled analyses of 3302 patients from seven randomized trials of 5-FU-based adjuvant therapy for stage II and III colon cancer, the only independent prognostic factors for DFS and OS were nodal status, tumor (T) stage and histological grade [Gill *et al.* 2004]. Univariate analysis demonstrated a 4% absolute risk reduction in DFS (HR, 0.82, $p=0.049$) but no improvement in mortality was observed (80% *versus* 81%, $p=0.1127$). When adjusted for T-stage, nodal status and grade, there was a 35% reduction in the risk of recurrence (HR, 0.65; 95% CI, 0.58–0.73) and a 30% reduction in the risk of death (HR, 0.73; 95% CI, 0.63–0.79) with adjuvant chemotherapy.

A systematic review focused on stage II patients was conducted by the Cancer Care Ontario Program in Evidence-based Care [Figueredo *et al.* 2004]. This review, which included 37 trials and 11 meta-analyses and was able to pool data from 4187 patients, found a risk ratio of 0.87 for adjuvant chemotherapy (95% CI, 0.75–1.01, $p=0.07$), representing a trend towards an improvement in OS.

Combination therapy

The MOSAIC trial demonstrated indubitable benefit in terms of DFS and OS for stage III colon patients. For stage II colon cancer, which represented 40% of the enrolled patients ($n=899$), 3-year DFS was 87% in the FOLFOX4 arm compared with 84.3% in the

5-FU/LV group (HR, 0.80; 95% CI, 0.56–1.15) [André *et al.* 2004]. Moreover, subgroup analysis of patients with high-risk features (T4 stage, perforation or obstruction, poorly differentiated tumor, lymphovascular invasion, fewer than 10 sampled lymph nodes) revealed a trend toward improvement in DFS for the combined treatment group (82.1% *versus* 74.9%; HR, 0.74; 95% CI, 0.52–1.06). However, the 6-year updated results of the MOSAIC trial showed no OS benefit by adding oxaliplatin for stage II patients regardless of their risk stratification [André *et al.* 2009].

Similar results from the NSABP C-07 trial demonstrated an overall benefit of the addition of oxaliplatin to 5-FU/LV but failed to demonstrate an improvement in the stage II patient population [Kuebler *et al.* 2007].

Recently, a large meta-analysis of adjuvant therapy for completely resected stage II colon cancer evaluated more than 7000 stage II patients included in 33 trials and 17 meta-analyses. The pooled risk ratio for OS and DFS were 0.96 (95% CI, 0.88–1.05) and 0.83 (95% CI, 0.75–0.92), respectively. Although there was no improvement in OS in the pooled analysis, adjuvant treatment significantly improved DFS of stage II colon cancer in this large database [Figueredo *et al.* 2008].

There is an ongoing trial that started on March 2008 with an estimated enrollment of 9500 patients, which will prospectively evaluate the role of combination chemotherapy after surgery in treating patients with high-risk stage II or stage III colorectal cancer. The results are expected and may definitively demonstrate the benefit of treatment in this patient population.

Adjuvant therapy in the elderly population

Incidence of colon cancer increases with age and the median age at diagnosis is 72 years. This patient population usually has more significant comorbidities and a higher incidence of noncancer-related deaths [Ades, 2009]. Thus, the risks and benefits must be weighted when considering adjuvant chemotherapy for the elderly colon cancer patient.

In a pooled analysis of seven phase III trials with 3351 patients, adjuvant therapy was associated with a 24% relative reduction in mortality (71% *versus* 64%, $p < 0.001$) and a 32% reduction in cancer recurrence ($p < 0.001$) for all age

subgroups (including age over 70 years), without an increase in adverse events in the elderly population [Sargent *et al.* 2001]. Additional data supporting survival benefit for postoperative chemotherapy for elderly patients was provided from a series of 4768 stage III colon cancer patients aged over 65 years. Although only 52% of eligible patients received therapy, the use of 5-FU-based chemotherapy was associated with a significant 34% reduction in mortality [Sundararajan *et al.* 2002]. A pooled analysis of 1567 patients (614 aged over 70 years) from four trials of the FOLFOX regimen showed similar benefits for all age subgroups [Goldberg *et al.* 2006].

In contrast to the above described results, recent analyses of data from the ACCENT database, with more than 12,500 patients enrolled in phase III trials of intravenous 5-FU compared with combination therapy or oral fluoropyrimidines, conclusively showed that patients aged over 70 years do not receive the same benefit from combination and/or oral FU as those under 70 years old.

Targeted agents for adjuvant therapy

Monoclonal antibodies against vascular endothelial growth factor and epidermal growth factor receptor (EGFR) are being increasingly recognized as important components of systemic therapy for metastatic colon cancer. Trials of targeted therapy combined with chemotherapy in the adjuvant setting have also been conducted [de Gramont *et al.* 2006].

The NSABP C-08 trial results were reported in the 2009 ASCO meeting [Wolmark *et al.* 2009]. In this trial, 2672 stage II (25%) and III patients were randomized to receive modified FOLFOX6 (mFOLFOX6) alone or plus bevacizumab (BEV). At a median follow up of 36 months, there was no significant DFS benefit for the addition of BEV (3-year DFS 77.4% *versus* 75.5%, HR for progression 0.89; 95% CI, 0.76–1.04).

In the recently completed phase III AVANT trial, high-risk stage II or stage III patients were randomized to FOLFOX4 *versus* FOLFOX4 plus BEV *versus* XELOX plus BEV. The safety analysis of this study was recently presented [Hoff *et al.* 2009] and the efficacy results are expected soon.

In addition, two phase III randomized trials (NCCTG/Intergroup N0147 and PETACC-8) are ongoing in evaluating the anti-EGFR

antibody, cetuximab, for the adjuvant treatment of stage III colon cancer. Preliminary data released to the press in November 2009 (unpublished) of the NCCTG/Intergroup N0147 trial indicated that the trial was negative, and that the endpoints could not be achieved. Therefore, at this time there seems to be no benefit from the addition of cetuximab to chemotherapy in the adjuvant setting of wild-type K-ras stage III colon cancer patients. The final report with the official results of this trial is expected soon.

Recommendations

Stage III colon cancer

For resected stage III colon cancer, adjuvant chemotherapy based on combined 5-FU/LV and oxaliplatin regimens should be the current standard of care because of the demonstrated benefit in DFS and OS for this patient population. To date there is no study directly comparing XELOX, FLOX, and FOLFOX and, therefore, there is no evidence to support recommendation of one specific protocol.

Stage II colon cancer

Adjuvant therapy should not be routinely recommended for unselected stage II colon cancer patients. However, because of a possible small absolute benefit with monotherapy, postoperative chemotherapy can be offered for medically fit high-risk stage II patients (T4 disease, fewer than 12 sampled lymph nodes, obstruction or perforated tumor, lymphovascular invasion, poorly differentiated histology). In this setting, monotherapy appears to have a better risk–benefit ratio and is the current recommendation, but combined therapy with oxaliplatin can also be discussed for selected cases.

Elderly patients

There is a general agreement that adjuvant therapy should be routinely offered for elderly patients. The optimal regimen for these patients is uncertain. Based on the recent results of the ACCENT database, patients over 70 years old do not benefit from combined oxaliplatin-based therapy. Therefore, we do not recommend routine use of combined adjuvant chemotherapy for elderly colon cancer patients. However, the risk–benefit ratio of combined treatment can be discussed and eventually recommended in very high-risk and otherwise healthy older patients.

Targeted agents

To date, there is still no role for targeted drugs in the adjuvant treatment of colon cancer. Results of ongoing trials may demonstrate benefit and further data are waited to define better the utility of these promising drugs on adjuvant setting.

Perspectives

Despite the important evolution and better understanding of the role of adjuvant therapy in stage II and III colon cancer, there are still several questions to be answered. Results of ongoing large prospective clinical trials are expected to refine the management and improve survival in this highly prevalent disease.

Conflicts of interest statement

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