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REVIEW ARTICLE

Adjuvant chemotherapy for high-risk stage II and stage III colon cancer: timing of initiation and optimal duration

Jan Paolo M. Cruz[1], Chris George C. Pales[2], Kwang Min Kim[3], Young Wan Kim[3]

[1]Division of Colorectal Surgery, Department of Surgery, Philippine General Hospital-University of the Philippines, Philippines; [2]Section of Colorectal Surgery, Department of Surgery, Southern Philippines Medical Center, Philippines; [3]Department of Surgery, Yonsei University Wonju College of Medicine, Wonju, Korea

Summary

The benefit of adjuvant chemotherapy has been clearly proven for patients with stage III (node-positive) and high-risk stage II colon cancer and consists to eradicating micrometastases that may be present during the time of surgical resection, reducing thereby the likelihood of disease recurrence and potentially increasing the cure rates after surgery. In this review, the appropriate timing of initiation and optimal duration of adjuvant chemotherapy are discussed. Current guidelines recommend an oxaliplatin-based regimen (FOLFOX: 5-fluorouracil with oxaliplatin or CapeOx: capecitabine with oxaliplatin) instead of 5-FU/LV (5-fluorouracil/leucovorin) for 6 months. For patients with a contraindication to oxaliplatin, a fluoropyrimidine-based regimen alone is an acceptable option. It should be initiated within 6-8 weeks from the time of surgical resection. Studies on reduced duration of fluoropyrimidine-based only regimens (bolus 5-FU/LV vs 5-FU) showed no significant difference in overall (OS) and disease free survival (DFS) benefits. However, the studies showed significantly lower toxicities for protracted venous infusion (PVI) 5-FU given for shorter duration. For oxaliplatin-based therapies, prospective trials failed to establish non-inferiority of 3 months compared to 6 months of oxaliplatin-based adjuvant therapy. The long-term data of the International Duration Evaluation of Adjuvant Chemotherapy (IDEA) collaboration for OS are not mature to date yet. Six months of oxaliplatin-based therapy still remain the standard of care. Decisions to shorten the duration of adjuvant oxaliplatin-based therapy should be dictated by drug tolerability, risk stratification of the disease, consideration of the value of decreased neurotoxicity at the cost of decreased DFS, and patient preference.

Key words: *adjuvant chemotherapy, capecitabine, colonic neoplasms, fluorouracil, oxaliplatin*

Introduction

For resectable non-metastatic colon cancer, the preferred surgical procedure is colectomy with *en bloc* removal of the regional lymph nodes. There has been recent attention focusing on the quality of colectomy. The principle of complete mesocolic excision (CME) has greatly improved outcomes of patients with colon cancer. It involves dissection through proper mesocolic planes with central vascular ligation, and sufficient proximal and distal margin lengths [1]. In a retrospective, population-based study (n=1395) by Bertelesen et al., CME was demonstrated to be oncologically superior to non-CME surgery based on 4-year DFS, of 85.8% vs 75.9%, respectively [1,2].

Correspondence to: Young Wan Kim, MD, PhD. Department of Surgery, Yonsei University Wonju College of Medicine, 20 Ilsan-ro, Wonju-si, Gangwon-do 26426, Wonju, Korea.
Tel: +82 33 741 0573, Fax: +82 33 742-0574, E-mail: youngwkim@yonsei.ac.kr
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For patients who have undergone potentially curative resection, the presence of undetectable or occult micrometastatic disease may be present even at the time of surgery. This may eventually result into clinical recurrence or relapse and even death of a substantial proportion of patients [2,3]. Increased cure rates may be achieved by administering adjuvant chemotherapy. Its benefits have been most clearly demonstrated in stage III (node-positive) disease, whereas benefit in stage II disease remains controversial [3].

There are still some issues of adjuvant chemotherapy following curative surgery in terms of appropriate timing of chemotherapy initiation and reduced duration of adjuvant chemotherapy. In this review, the appropriate timing of initiation and optimal duration of adjuvant chemotherapy are discussed.

Timing of initiation

A systematic review and meta-analysis of 10 studies, that included 15,410 patients, examined the effect of timing of adjuvant therapy after resection. This meta-analysis showed that each 4-week delay to adjuvant chemotherapy initiation was associated with a significant decrease in OS by approximately 14%, as well as the DFS rate [3,4]. A retrospective study of 6620 patients with stage III colon cancer from the Netherlands Cancer Registry showed that commencing adjuvant chemotherapy beyond 8 weeks was associated with decreased OS compared to initiation within 8 weeks [Hazard ratio (HR) 9–10 vs ≤8 weeks 1.4 (1.21–1.68); HR 11–12 vs ≤8 weeks 1.3 (1.06–1.59) and HR 13–16 vs ≤8 weeks 1.7 (1.23–2.23)] [4]. Currently, there is no agreement on the specific optimal time to initiate adjuvant chemotherapy, but is generally accepted that adjuvant therapy should be administered as soon as the patient is medically fit for chemotherapy, usually within 6-8 weeks after surgery [3-5].

The interval between surgery and start of chemotherapy usually takes longer than 8 weeks in clinical practice. The reasons implicated are usually multifactorial and vary among institutions: wound healing and recovery from surgery, advanced age with greater levels of comorbidities, lower socioeconomic status, inefficiencies of healthcare systems, medical aid status in the health security system (insurances), and lack of social support [4-8].

Duration of therapy

The issue about the reduction of the duration of adjuvant chemotherapy is controversial. The optimal duration of adjuvant chemotherapy for patients with high-risk colon cancer has evolved over the previous decades. One-year treatment has been recommended during the early 1980s, but subsequent studies showed equivalent efficacies for 6 months of treatment [9]. The ability to maintain the efficacy of treatment with possibly reduced toxicities of a reduced duration of therapy would clearly be advantageous to individual patients, health care systems and providers, resulting to better compliance to treatment and better allocation of healthcare resources.

Fluoropyrimidine-based therapies

The efficacy of adjuvant therapy utilizing 5-FU/LV was initially based on studies for 12 months of treatment. Subsequent trials showed a comparable efficacy of 6 months to 12 months therapy of 5-FU/LV. The Intergroup 0089 trial randomized 3,794 patients into four treatment subgroups: high-dose 5-FU/LV (HDLV), low-dose 5-FU/LV (LDLV) and low-dose levamisole plus 5-FU (LDLV plus LEV) for 6 to 8 months, and levamisole plus 5-FU for 1 year. The study showed that the efficacy was not significantly different between the 6 to 8 months therapy compared to 12 months, without the additional toxicity. Overall, greater toxicity was more frequently for the LDLV and the LDLV plus LEV patients. Overall toxicity was not significantly different between the HDLV arm and the LEV, but LDLV plus LEV was significantly more toxic than LDLV [10]. Furthermore, the GERCORE (Groupe d'Etude et de Recherche Clinique en Oncologie Radiotherapie) trial showed that the 6-month 5-FU/LV regimen was as effective as 9 months and 1 year of 5-FU/LV [11].

The randomized clinical trial conducted by Chau et al. compared the efficacy and toxicity of 3 months of protracted venous infusion (PVI) 5-FU against the standard bolus monthly regimen of 5-FU/LV given for 6 months. There was no significant difference in OS between the two treatment groups. The probability of 12 weeks of PVI 5-FU being inferior to 6 months of bolus 5-FU/LV was extremely low ($p<0.005$). Significantly less diarrhea, stomatitis, nausea, vomiting, alopecia, lethargy, and neutropenia (all $p<0.0001$) were observed with PVI 5-FU patients [12]. A similar multi-center randomized clinical trial study conducted by Saini et al. showed that OS did not differ significantly ($p=0.764$) between patients receiving 5-FU/LV and PVI 5-FU (3-year survival 83.2 vs 87.9%, respectively). On the other hand, patients in the 5-FU/LV group had significantly worse relapse-free survival ($p<0.023$) compared to those receiving PVI 5-FU (3-year RFS 68.6 vs 80%, respectively). Grades 3-4

neutropenia, diarrhea, stomatitis and severe alopecia were significantly less (p<0.0001) for patients in the PVI 5-FU treatment arm [13].

Oxaliplatin-based therapies

The standard FOLFOX regimen, generally based on the MOSAIC trial, showed that 6 months of FOLFOX treatment had a significantly higher 6-year OS in stage III disease compared with 5-FU alone (73 vs 69%) [14]. Unfortunately, despite being the standard of care, 6 months of oxaliplatin-based therapies had adverse effects, particularly neurotoxicity, which impaired significantly the quality of life and activities of daily living in a dose-dependent manner. Kumar et al. conducted a retrospective population-based analysis of patients receiving adjuvant FOLFOX for stage III colon cancer in Canada. There was no significant difference in both OS for patients who received ≥ 10 compared to <10 cycles (78 vs 77%, p=0.99) and 3-year DFS (81 vs 81% respectively, p=0.995). The 10-cycle cutoff was selected to provide comparable group sizes to facilitate a robust statistical analysis. In this light, it does not evaluate outcome differences between the guideline recommendations of 12 cycles vs less than that [15].

A retrospective descriptive observational cohort study was conducted by Tsai et al. in Taiwan aimed to find the appropriate number of treatment cycles of mFOLFOX6 that would give the most survival benefit. Among the 213 patients analyzed, a significant benefit was noted for OS with a treatment of at least 8 cycles. On the other hand, for DFS, significant differences were apparent with 7 to 12 treatment cycles [16].

The IDEA Collaboration

The International Duration Evaluation of Adjuvant Chemotherapy (IDEA) collaboration wasestablished to prospectively combine and interpret data from 6 different clinical trials from 12 different countries worldwide to determine whether 3-month course of oxaliplatin-based adjuvant therapy is non-inferior to 6-month course and to assess how much efficacy can be compromised to achieve lower toxicity [17]. The type of chemotherapy regimen given was not randomized and was based mainly on the physicians' choice (FOLFOX4, mFOLFOX6, CapeOx). Table 1 shows the details of the different participants of the IDEA collaboration. The study included 12,834 patients from 12 countries with data collected from 2007 to 2015. Full text publications of the results of the individual trials and pooled data are still pending. Based on the abstract review of the presentation of the IDEA collaboration at the American Society of Clinical Oncology Meeting last June 4, 2017, overall, the 3-year DFS rate was 74.6% (3 months) and 75.5% (6 months), with estimated DFS HR of 1.07. The 3-month vs 6-month DFS HRs were 1.16 (1.06-1.26) and 0.95 (0.85-1.06) for FOLFOX and CapeOx treated patients respectively (p=0.0051). The 3-month vs 6-month DFS HRs were 1.01 in T1-3 or N1 patients, and 1.12 for T4 or N2 patients (p=0.11). Grade 3 and higher neurotoxicity was higher in the 6-month vs the 3-month arm (16 vs 3% FOLFOX, 9 vs 3% CapeOx, p<0.0001). With these data, the non-inferiority was not established for the overall cohort. The non-inferiority of 3 vs 6 months adjuvant therapy was supported for CapeOx. It was established that shorter duration decreased toxicities. The collaboration recommends a risk-based approach to treatment: patients with low risk stage III cancers (T1-3 or N1) may not require >3 months adjuvant treatment, and those given CapeOx may be given just 3 months adjuvant therapy independent of tumor stage [18]. Table 2 summarizes the studies showing the effect of reduction of duration to survival benefit and adverse events.

Table 1. IDEA Collaboration

Trial	*Location*	*Chemotherapy regimen*	*Number of patients (Total = 12,834)*
TOSCA	Italy	CapeOx or FOLFOX4	2402
SCOT	United Kingdom, Denmark, Spain, Sweden, New Zealand, Australia	CapeOx or mFOLFOX6	3983
IDEA France	France	CapeOx or mFOLFOX6	2010
CALGB/SWOG	United States, Canada	mFOLFOX6	2440
HORG	Greece	CapeOx or FOLFOX4	708
ACHIEVE	Japan	CapeOx or mFOLFOX6	1291

IDEA: International duration evaluation of adjuvant chemotherapy, TOSCA: Three Or Six Colon Adjuvant, CapeOx: Capecitabine with oxaliplatin, FOLFOX: 5-fluoropyrimidine with oxaliplatin, SCOT: Short course oncology treatment, CALB: Cancer and Leukemia Group B, SWOG: Southwest Oncology Group, HORG: Hellenic Oncology Research Group, ACHIEVE: Adjuvant Chemotherapy for colon cancer with High EVidence.

Table 2. Effect of reduced duration of chemotherapy to survival benefit and adverse events

Trial/ Authors	*Year*	*Study period*	*Number of patients*	*Chemotherapy regimen*	*Duration*	*Survival benefit*	*Adverse effects*
Intergroup 0089							
Haller et al. [10]	2005	1988-1992	3794	LDLV HDLV LDLV+LEV LEV	6-8 months (LDLV, HDLV, LDLV+LEV) vs 1 year (LEV)	5 year OS LDLV: 60% HDLV: 58% LDLV+LEV: 49% LEV 55%	Neurologic- LDLV: 1.4%/ HDLV: 1.5%/ LDLV + LEV: 3.0%/ LEV: 4.8% Stomatitis- LDLV: 14.7%/ HDLV: 1.0%/ LDLV + LEV: 17.3%/ LEV: 2.8% Diarrhea- LDLV: 12.2%/ HDLV: 15.4%/ LDLV + LEV: 10.4%/ LEV: 7.2% Granulocytopenia- LDLV: 8.6%/ HDLV: 2.0%/ LDLV + LEV: 10.9%/ LEV: 7.5%
GENCORE trial							
Andre et al. [11]	2007	1996-1999	905	LV5FU2 vs Bolus mFU/LV	6 months vs 9 months	6 year DFS- LV5FU2: 66%/ mFU/LV: 65% (P= 0.74)	N/A
Saini et al. [13]	2003	Not specified	716	Infusion 5-FU vs Bolus 5-FU/LV	3 months (5-FU) vs 6 months (5-FU/LV)	3 year OS- Infusion 5-FU: 87.9% / Bolus 5-FU/LV: 83.2% (P=0.764) 3 year DFS- Infusion 5-FU: 80% / Bolus 5-FU/LV: 68.6% (P=0.23)	Neutropenia- 5-FU: 0.9%/ Bolus 5-FU/ LV: 55.6% (P <0.0001) Diarrhea- 5-FU: 5.4%/ Bolus 5-FU/LV: 16.0% (P <0.0001) Stomatitis- 5-FU: 3.6%/ Bolus 5-FU/ LV: 19.6% (P <0.0001) Alopecia- 5-FU: 0.3%/ Bolus 5-FU/LV: 14.3% (P<0.0001)
Chau et al. [12]	2005	1993-2003	801	PVI 5-FU vs Bolus 5-FU/LV	3 months (PVI 5-FU) vs 6 months (Bolus 5-FU/ LV)	5 year OS- PVI 5-FU: 75.7% / Bolus 5-FU/ LV: 71.5% (P=0.083) 5 year DFS- PVI 5-FU: 73.3% / Bolus 5-FU/ LV: 66.7% (P= 0.1)	Neutropenia- PVI 5-FU: 16.3%/ Bolus 5-FU/LV: 82.5% (P <0.0001) Diarrhea- PVI 5-FU: 54.9%/ Bolus 5-FU/LV: 77.3% (P <0.0001) Leucopenia- PVI 5-FU: 15.5%/ Bolus 5-FU/LV: 65.5% (P <0.0001) Stomatitis- PVI 5-FU: 53.8%/ Bolus 5-FU/LV: 77.7% (P <0.0001) Alopecia- PVI 5-FU: 14.0%/ Bolus 5-FU/LV: 47.7% (P <0.0001)
Kumar et al. [15]	2015	2006-2010	616	FOLFOX	≥10 cycles vs <10 cycles	3 year OS- ≥10 cycles: 78%/ <10 cycles: 77% (P=0.99) 3 year DFS- ≥10 cycles: 81% / <10 cycles: 81% (P= 0.995)	N/A
Tsai et al. [16]	2016	2005-2012	692	mFOLFOX6	1 to 12 cutoff cycles	OS: ≥8 cycles vs <8 cycles (statistically significanct) DFS: 7-12 cycles vs <7 cycles (statistically significanct)	N/A
IDEA Collaboration							
(abstract review of ASCO 2017 presentation) [18]	2017	2007-2012	12,834	FOLFOX4 mFOLFOX6 CapeOx	3 months vs 6 months	3 year DFS (3 months vs 6 months) HR by risk group T1-3 or N1: 1.01 T4 or N2: 1.12 (P=0.11) HR by regimen FOLFOX: 1.10 CapeOx: 0.95 (P=0.0051)	Grade 3 and higher neurotoxicity FOLFOX-6 month: 16%/ 3 months: 3% (P< 0.0001) CapeOx- 6 month: 9%/ 3 months: 3% (P < 0.0001)

LDLV: low-dose leucovorin, HDLV: high-dose leucovorin, LEV: levimasole, OS: overall survival, LV5FU2: continuous leucovorin infusion plus bolus 5-FU, mFU/LV: 15-f minute leucovorin infusion plus 5-FU, DFS: disease free survival, PVI: peripheral venous infusion, FOLFOX: 5-FU, oxaliplatin and leucovorin, IDEA: International Duration Evaluation of Adjuvant Chemotherapy, ASCO: American Society of Clinical Oncology, N/A: not applicable

Discussion

The goal of adjuvant therapy is to eradicate micrometastases that may be present even during the time of surgical resection to reduce the likelihood of disease recurrence and potentially to increase cure rates in patients who underwent curative resection for colon cancer. The benefit is clearly proven for those with stage III (node-positive) and high-risk stage II disease. Current guidelines recommend an oxaliplatin-based regimen (FOLFOX or CapeOx) instead of 5-FU/LV for 6 months. However, for patients with a contraindication to oxaliplatin or those who are unlikely to tolerate oxaliplatin, such as those with pre-existing neuropathy, a fluoropyrimidine-based regimen alone is an acceptable option. However, survival outcomes may not be as favorable as compared to an oxaliplatin-based regimen.

Adjuvant therapy should be initiated within 6-8 weeks from the time of surgical resection. Varying factors such as wound healing and recovery from surgery, advanced age with greater numbers of comorbidities, lower socioeconomic status, inefficiencies of healthcare systems, medical aid status in the health security system, insurances, and lack of social support cause delay of the initiation of adjuvant therapy.

The optimal duration of adjuvant chemotherapy is controversial and evolving. The ability to maintain the efficacy of treatment with possibly reduced toxicities of a reduced duration of therapy would clearly be advantageous to individual patients, healthcare systems and providers. The studies on reduced duration of fluoropyrimidine-based only regimens (bolus 5-FU/LV vs PVI 5-FU) showed no significant difference in OS and DFS benefits. However, the studies showed significantly lower toxicities (diarrhea, stomatitis, severe alopecia, neutropenia, etc.) for PVI 5-FU given for less duration. For oxaliplatin-based therapies, 6 months of therapy are recommended. Prospective trials failed to establish non-inferiority of 3 months compared to 6 months of oxaliplatin-based adjuvant therapy. Decisions to shorten the duration of adjuvant oxaliplatin-based therapy should be dictated by drug tolerability, risk stratification of the disease, consideration of the value of decreased neurotoxicity at the cost of decreased DFS, and patient preference. The preliminary analysis of the IDEA collaboration presented at the ASCO meeting last June 4, 2017, did not establish non-inferiority, but showed only a small predicted loss of DFS benefit and significantly lower rates of oxaliplatin-related neuropathy. Guided by this, it seems reasonable to restrict adjuvant therapy to 3 months in patients with low-risk disease (T1-3,N1). On the other hand, those with high-risk disease (T4,N2) should still undergo treatment for 6 months. The collaboration also suggests that CapeOx may be given for 3 months only, independent of the T and N status of disease. However, these are all preliminary data, the full publications of the results of the individual trials and the pooled data are still pending. Furthermore, the long-term OS data are not mature yet. Although 3-year DFS is a validated surrogate endpoint for OS, longer-term data are needed to show the robustness of these results. Therefore, these recommendations are not absolute. Patients with low-risk disease (T1-3, N1) who want to minimize their risk of disease recurrence, still have to choose a standard 6-month adjuvant therapy rather than a shortened 3-month treatment. Patients with higher-risk disease, who wish to avoid the potential adverse effects such as neurotoxicity, may choose 3 months of therapy if they understand and are willing to accept a small potential detriment in DFS. In the interim, 6 months of oxaliplatin-based therapy still remains the standard of care.

Conclusions

There is still room for improving adjuvant treatment for stage III and high-risk stage II colon cancer. There are still few studies about the appropriate timing of initiation and the optimal duration of adjuvant chemotherapy. Patients should be well-informed of the current adjuvant therapy guidelines and evidence before administration. Tailored modification of chemotherapy dosage and schedule should be based on current evidence, risk stratification of disease, drug toxicities and tolerability, but should also consider patient preference.

Contributions

JPC and YWK conceived the study concept and participated in its design, data extraction, statistical analysis, and manuscript drafting and editing. CGP and KMK participated in conceiving the study concept and participated in the design and editing. All authors read and approved the final manuscript.

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Conflict of interests

The authors declare no conflict of interests.

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