Chapter 13

Adjuvant Treatment in Colon Cancer

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Abstract

Worldwide, more than 1 million people develop colorectal cancer (CRC) annually. CRC is a major health problem in the Western world and the second most common cause of cancer mortality. To improve performance, the role of chemotherapy for CRC has increased dramatically over the last decade. The vast majority of CRC patients now receive chemotherapy with multiple agents that are currently approved for the treatment in the appropriate setting [1]. However, it is a complex process to select the optimal chemotherapy for each patient and practice evidence gap is still a problem. Some guidelines for the treatment of CRC have been developed to promote the standardization of CRC treatment. Postoperative, or "adjuvant," systemic therapy has become standard for stage III colon cancer. Adjuvant therapy should also be strongly considered in stage II patients. It is generally recommended for any medically fit patient with stage II cancer with unfavorable factors. The hypothesis that the antitumor activity of the combination agent, including oxaliplatin, irinotecan, bevacizumab, cetuximab in metastatic cure rates, would result in increased adjuvant proved to be often wrong. Although new drug development takes years, targeted drug use can occur more quickly with advanced tests and will be a focus of future work. In addition, efforts will focus on identifying biomarkers that predict response to systemic therapy so that tailored therapy can be initiated. The future of oncology will come with the better understanding of the biology and genetics of the tumor and its host. This will help to develop tailored approach to the patients, including more specific systemic therapy, aimed at molecular targets of the malignant tumor, thus reducing the negative effects. At that time, the treatment of oncological diseases will experience a new era, comparable to the introduction of antibiotics.

Keywords: Chemotherapy, Adjuvant treatment, Colon cancer

1. Introduction

Colorectal cancer develops in more than 1 million people every year. This is a major health problem and a second of frequency cause of mortality by cancer. The mortality from CRC has decreased by almost 35% for 17 years and the reasons are early diagnosis, new screening programs and treatment principles. Surgery is the basic of the initial treatment, but the next step on treatment in most of patients with CRC is adjuvant chemotherapy. Adjuvant chemotherapy decreases the risk of following metastatic dissemination. This systemic treatment aims eradication of disseminated microscopic tumor cells, control of development of the primary tumor and the tumor extension. The histologic stage of the tumor at the time of resection determined the 5-year survival rate of CRC patients. The most important factor for survival in patients with CRC and without metastatic disease is the stage of the tumor. The stage of the tumor responds to depth of the tumor penetration through the intestinal wall (*T*) and the number of lymph nodes with invasion (*N*). 14% decrease of overall survival is because of systemic treatment. Because of this it is considered to start adjuvant chemotherapy as soon as possible.

Oral fluoropyrimidines, oxaliplatin, and irinotecan added to 5-FU chemotherapy (CT) led to good results about progression-free survival (PFS), response rate, and overall survival (OS) in patients with metastatic colorectal cancer. This statement is subject to the clinical trial about the adjuvant setting of non-metastatic disease in patients with stage III tumors. The adjuvant CT regimens used often in oncology are shown in **Table 1**.

Name	Protocol
5FU/LV (bolus)	Mayo clinic regimen
LV5FU2	LV 200 mg/m^2, 5FU 400 mg/m^2 bolus followed by 5FU 600 mg/m^2 22-h infusion, given every 14 days for 12 cycles
Capacetabine	Capacetabine 1250 mg/m^2 twice daily for 14 days every 3 weeks
FLOX	5FU 500 mg/m^2 bolus every week for 6 weeks, LV 500 mg/m^2 every week for 6 weeks of 8 week cycle, for 3 cycles + oxaliplatin 85 mg/m^2 on week 1, 3, 5 of each cycle
mFOLFOX6	LV 400 mg/m^2 IV on day 1, 5 FU 400 mg/m^2 IV bolus on day 1 followed by 2400 mg/m^2 by continuous infusion over 46 h (day 1 and 2); oxaliplatin 85 mg/m^2 IV day 1;every 14 days for 12 cycles
FOLFOX4	LV5FU2 + oxaliplatin 85 mg/m^2 on day 1 (with LV)

Abbreviations: 5FU = 5 fluorouracil; IV = intravenous; LV = leucovorin

Table 1. Different regimens used for adjuvant chemotherapy in colorectal cancer.

In patients with stage II colon cancer surgery alone is usually curative but in 20–30% of them there is tumor recurrence and metastatic disease. The chemotherapy has side effects in patients and some of them change survival rate. The studies found markers for prediction of return the disease. This marker is useful in stage II colorectal cancer. The studies about adjuvant therapy

and stage of the tumor show that cytotoxic therapy has more in stage II of CRC. In the future, should be handled with the direction to find more specific markers for precise selection [1].

Data for colon cancer genesis and metastasis in lymph node show that CXC chemokine receptor type 7 (CXCR7) had role in these processes. The study about this in group of 34 patients at age between 34 and 79 years with malignant colon pathology and second group of 18 patients with normal colon tissue. CXCR7 levels were higher in group with colon tumors, 20 cause of this group was presented with lymph node metastases. There are an evidence for involvement of the upregulated CXCR7 expression in colon cancer and lymph node metastasis [10].

MSI is a change in the length of DNA microsatellites caused by insertion or deletion of repeated units (1–5 nucleotides), due to defects in mismatch repair genes or methylation of their promoters. Tumors with MSI are proximal, poorly differentiated, and mucinous. This tumors show marked lymphocyte infiltration. Colon cancers with high-frequency of MSI have clinical and pathological differences from microsatellite-stable tumors; thus colon cancer patients stage II or III with microsatellite-stable tumors or tumors exhibiting high-frequency microsatellite instability have favorable outcome. Therefore MSI is a predictor for decreased benefit of Fluorouracil-based adjuvant chemotherapy. MMR protein deficiency and MSI can cause by silencing or mutation of mismatch repair (MMR) genes [2]. This condition occurs in patients with Lynch syndrome and is a rare cause for hereditary colon cancer: 2–4% of all cases. Somatic mutation can found in 19% of CRC and 52% of sporadic colon cancer has silencing of MMR genes. There are three groups in sporadic CRC—microsatellite stable (MSS), low-frequency MSI (MSI-L), and high-frequency MSI (MSI-H). MSI-H is frequently found in stage II disease. This confirms a data about the decreased use from 5FU adjuvant chemotherapy in patients with colon cancer stage II disease.

In contrast to this, it was shown in recent studies of more than 2000 patients. This study proved that MSI-H status was prognostic but not predictive of benefit or detrimental impact of adjuvant chemotherapy [3]. Tests for discovery MSI in colorectal cancer for ≤70 years:

1. immunohistochemical tests for MMR protein producing;
2. for changes in the length of repetitive DNA elements in tumor tissue due to insertion or deletion [4, 5].

Starting a development of several multigenes such as Oncotype DX with purpose to identify which patient would have a great help from adjuvant CT. In this trial patient's chance of recurrence was classified in three groups—low, intermediate and high. Recurrence score was calculated by the evaluation of a panel of 12 genes—7 recurrences cancer-related and 5 reference genes [1, 8]. The statistical analysis clarifies that recurrence DFS and OS score of recurrence of disease correlated with disease relapse. Relapse of disease depends of TNM staging, MSI, number of histologically examined lymph nodes and tumor grade.

That result of multigene analysis could not predict a help for patient of adjuvant CT.

2. Treatment guidelines for adjuvant chemotherapy

2.1. 5 FU

The value of adjuvant CT in patients with stage III colon cancer is first reported in 1990 by Moertel and colleagues (Dukes C, TxN+M0). Comparing between adjuvant 5-FU/levamisole chemotherapy for 1 year, levamisole alone and without chemotherapy showed an increase in OS and PFS in patients receiving first model of chemotherapy. 5FU is a pyrimidine analog, inhibitor of enzyme thymidylate synthase (TS) (involved in de novo synthesis of thymidine) and is involved in the process of incorporation of nucleotides into RNA and DNA, leading to inhibition of DNA synthesis and function. Continuous infusion of 5FU is 100–1000 times lower than the concentrations if injected i.v. bolus. In second way 5FU reaches a maximum plasma and bone marrow concentration [7, 9].

There is information that the expression of E2F1, which control the transcription of genes encoding proteins engaged in DNA synthesis including TS. A study examined the relationship between E2F1 and TS expression in patients with colon cancer and the effect of 5 FU. It showed that the combined E2F1/TS immunophenotype could be a potential indicator for sensitivity of patients on adjuvant chemotherapy with 5FU [11].

Over 85% of the drug is inactivated in metabolic processes by the enzyme dihydropyrimidine dehydrogenase (DPD). DPD synthesize by the liver. Some mutations in DPD can found in approximately 2% of the general population. This can cause serious life-threatening toxicity in patients. Leucovorin (LV, folic acid) intensifies the antitumor activity of 5FU. Treatment without LV is still a reasonable option.

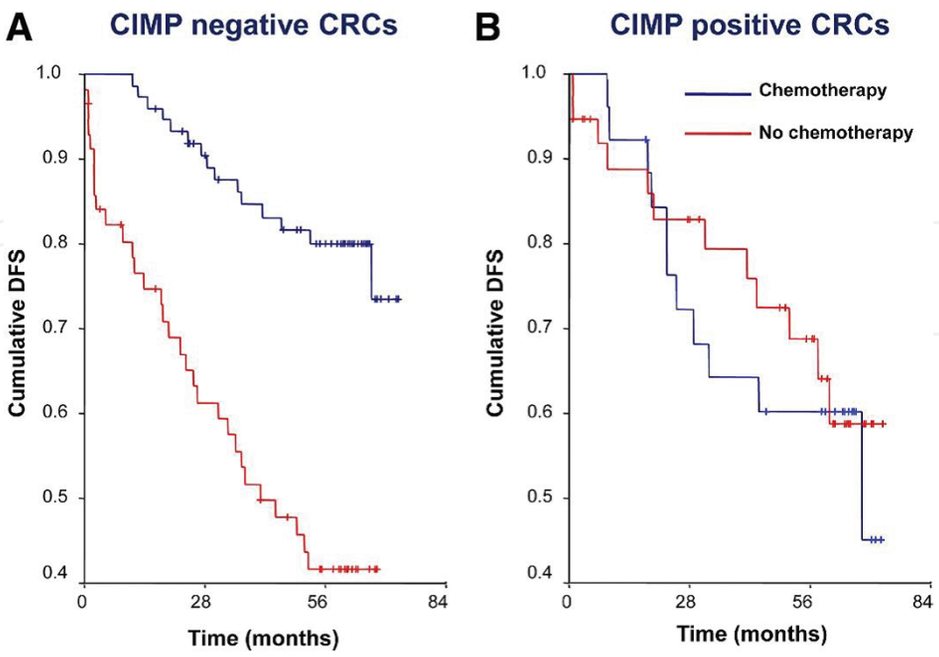

Figure 1. Comparison between CIMP negative and CIMP positive in relation to the effects of chemotherapy [12].

Rodrigo Jover and all explored effect of 5FU chemotherapy in patients with CRC. Their study included group of patients with CpG island methylator phenotype (CIMP) colorectal cancer and analyze a response of patients with this mutation. CIMP status was determined by analysis of the CACNAG1, SOCS1, RUNX3, NEUROG1, and MLH1 promoters. Tumors were CIMP positive when they had 3 promoters methylated. Result of study shows that patients with CIMP positive colorectal cancer do not have a benefit from adjuvant chemotherapy with 5-fluorouracil regarding to survival time [12] **Figure 1**.

Analysis of the data from several trials in which patients randomly received only tumor resection or tumor resection and adjuvant 5FU/LV, showed that benefit of adjuvant CT was observed in stage III patients [1]. These patients have higher risk because of the metastatic regional node.

In patients with stage T3 or T4 resectable rectal cancer treatment is with preoperative radiotherapy with or without simultaneous chemotherapy. In randomized study in patients with rectal cancer after surgery they start adjuvant chemotherapy or are on dispensary and monitored. Radiotherapy including 45 Gy to the posterior pelvis in 25 fractions of 18 Gy over 5 weeks and the courses of chemotherapy had fluorouracil and folinic acid. For preoperative chemotherapy, two courses were given (during weeks 1 and 5 of radiotherapy). Adjuvant chemotherapy was given in four cycles, every 3 weeks. Conclusion of this study can show that adjuvant fluorouracil-based chemotherapy after preoperative radiotherapy (with or without chemotherapy) does not affect disease-free survival or overall survival [13].

5FU/LV plus oxaliplatin as adjuvant treatment is used in stage II colorectal cancer. The study on group of elderly patients show no importance DPS or OS benefit even in this causes with high risk characteristics—T4 tumors, bowel obstruction, venous invasion etc. 5FU/LV stay the preferred adjuvant chemotherapy regimen.

5-Fluorouracil (5FU)-based chemotherapy (CT) remains the mainstay treatment of CRC and activates executioner caspases in target cells. Executioner caspases are key proteins involved in cell disassembly during apoptosis. Their activation also has a role in tissue regeneration and repopulation by stimulating signal transduction and cell proliferation. A study about this proteins and 5FU-based chemotherapy shows that patients with low levels of active caspase-3 had an increased disease-free survival time. Lower serum levels of active caspase-3 were found in patients with metastasized CRC. This indicates that low levels of active caspase-3 may be a new predictor of CT responsiveness. Inhibition of caspase-3 may be a marker for improve patient outcomes following CT in advanced CRC [14].

2.2. Oral fluoropyrimidines

Two oral prodrugs of 5FU—capecitabine and Uracil/tegafur (UFT) showed efficacy in the metastatic setting, as compared to 5FU/LV bolus regimens. Capecitabine is oral administration, rapidly absorbed with peak blood levels after 1.5 h [1]. Capecitabine is contraindicated in patients with severe renal impairment (creatinine clearance below 30 mL/min).

Adjuvant therapy for patients with resected stage III colon cancer includes i.v. bolus regimen of 5FU/LV, and oral capecitabine is unsuitable. Taking a capecitabine has rarely occurring symptoms of diarrhea, stomatitis, nausea, alopecia, neutropenia, and febrile neutropenia [6].

3. Combination adjuvant therapies

The benefits of adjuvant chemotherapy by combinations with drugs—oxaliplatin, irinotecan, bevacizumab, or cetuximab in the metastatic disease—were not confirmed. Oxaliplatin is a third-generation platinum compound and reported that its safety administration with evidence for clinical activity, because ability to develop a covalent adducts with cellular DNA. Study for oxaliplatin examined platinum in the body for 8–75 months after treatment with cisplatin and oxaliplatin, because of time to excretion. Therapeutic index of oxaliplatin is limited. Adverse reactions from this treatment are symptoms in the peripheral nerves, the hematopoietic and the gastrointestinal system.

In the adjuvant chemotherapy the addition of oxaliplatin can improve patient outcomes. The MOSAIC trial explores 2246 patients with stage II or III CRC. They take LV/5FU2 or FOLFOX-4 (LV/5FU2 + oxaliplatin).

The results are summarized in **Table 2**.

	FOLFOX (%)	5FULV2 (%)	P value
5-year DPS (sage II + III)	73.3	67.4	0.003
6-year OS (stage II + III)	78.5	76.0	0.046
6-years OS (stage III only)	72.9	68.7	0.023
6-years OS (stage II only)	85	83.3	0.65
Grade 3-4 neutropenia	41	5	
Grade 3-4 diarrhea	11	7	
Grade 3 neuropathy	12	0	

Unfortunately the side effects are more frequent.

Table 2. The FOLFOX regimen has significantly better oncological results compared to 5FULV2.

In conclusion, FOLFOX-4 is more toxic than separately LV/5FU2. The mortality in the first 60 days has close rate [2].

Multicenter AGEO Study assessed the efficacy of adjuvant chemotherapy with fluoropyrimidine with and without oxaliplatin. And results support other conclusion that there is a benefit from the combined application of fluoropyrimidine and oxaliplatin in patients with colon cancer stage III with deficient mismatch repair (dMMR).

The NSABP C-07 and the MOSAIC trials had a similar purpose, but used different plans to treatment. In one of trials used FLOX regimen—oxaliplatin was given on weeks 1, 3, and 5

plus weekly and bolus 5FU/LV on weeks 1 through 6. This is 8 weeks cycle. The results compared with standard use of 5FU/LV. More than 2000 patients received FLOX or 5FU/LV treatment. All of patients were classified into two groups—stage II patients (29%) and stage III patients (71%). The research is for 34 months. Results of this study showed benefit in the short 7-year term, but then in long term, there was no difference in the results between the two groups.

The MOSAIC and NSABP C-07 trials make research for oxaliplatin but with different doses. Their small positive results improved a benefit of oxaliplatin to chemotherapy in patients with stage II disease. But this is not enough to justify given outcomes and the risk of neurotoxicity.

Phase III of trial, which aim was to comparing capecitabine plus oxaliplatin (XELOX) with bolus 5FU/LV as adjuvant therapy for stage III colon cancer proved that XELOX had an improved 3-year DFS rate compared with 5FU/LV. Patients with XELOX had less frequently diarrhea or alopecia but occurred more vomiting, neurosensory toxicity, and hand–foot syndrome. All trials showed that FOLFOX, FLOX and XELOX could all be with equal value when they used in the adjuvant setting [3].

Irinotecan is a semisynthetic analog of camptothecin, first isolated from the Chinese/Tibetan ornamental tree Camptotheca acuminata. It is a chemotherapy agent that causes S-phase-specific cell killing by poisoning the enzyme topoisomerase I in the cell [4].

PETACC-3 investigators also investigate how add of irinotecan to adjuvant LV/5FU2 would improve status of patients with colon cancer. They observed that patients with irinotecan to LV/5FU2 had an increased frequency of adverse reaction and neutropenia. In conclusion of this trial, irinotecan in combination with LV/5FU2 as adjuvant therapy did not show benefits in patients with stage III colon cancer [5]. Using irinotecan in the adjuvant setting in stage II and III patients did not support with data. Analysis of PETACC-3 trial could not justify the expected benefit from administration of irinotecan to LV/5FU2. Bevacizumab is a recombinant, humanized monoclonal antibody against the vascular endothelial growth factor (VEGF), inhibitor of VEGF function in vascular endothelial cells and thereby inhibits the tumor neoangiogenesis, upon which solid tumors depend on growth and metastasis [3, 6]. Bevacizumab demonstrated positive impact added to standard CT in the metastatic disease.

Cetuximab is a monoclonal antibody which upon binding to the transmembrane epidermal growth factor receptor (EGFR). EGFR controls many important tumor cell functions including tumor growth, neoangiogenesis, inhibition of the apoptotic response to chemotherapy, and radiotherapy. Cetuximab realize inhibition and degradation [3].

There are reports from last years about drug screening system, which is based on nanoimprinting 3-dimensional (3D) culture. It is use to predict effectiveness of new chemotherapeutic drugs. Also with this system can find the most effective agent for colon cancer. A research in this area examines the benefit from treatment with regorafenib on a mouse model in vivo. Result from this study was based on new nanoimprinting 3D culture and it shows that regorafenib is on track to be the most effective drug. In study were compared this agent and 5 FU and in conclusion regorafenib may be the most effective adjuvant therapy for colon cancer in the future [15].

4. Adjuvant therapy for resectable metastatic disease

Patients with metastatic disease who are subjected to liver or lung resection is first submitted to active systemic chemotherapy. The therapy should not be more than 6 months.

Regimens recommended that resectable metastatic disease and non-metastatic disease had a similar adjuvant setting.

5. Adjuvant CT for elderly patients

Colon cancer in most of the cases is diagnosed in patients >70 years in USA. The purpose and aim of oncology is to give patients aged >75 years longer life than they expected. Adjuvant therapy gave a survival advantage in younger and older patients. There is a discussion about safety and efficacy of the treatment in elderly and younger patients, but analysis showed that there are certain toxicity rates and similar advantage for survival. The most of data about adjuvant therapy is from trial on elderly patients and without new therapeutic agents such as oxaliplatin [3].

The study which purpose is to show benefits from adjuvant chemotherapy for patients ≥75 years of age with resected stage III colon cancer (CC) presented that adjuvant chemotherapy does not show the expected result. Oxaliplatin offers small incremental. The use of adjuvant chemotherapy after the age of 75 years should be assessed individually [16].

The results of a study indicate that patients aged >75 years represent nearly 20% of all cases with lymph node-positive colon cancer although the majority of recommendations limit colorectal cancer screening to individuals aged u years. Older age was associated with much lower rates of adjuvant chemotherapy administration, whereas the survival benefits of such treatment remain comparable to those of younger patients with stage III colon cancer. This statement is established on large population-based study. There are a lot of trials and data for adjuvant chemotherapy, but optimal and efficient strategy is not established. More research needed to understand which benefit is bigger from administration of adjuvant treatment after surgical resection.

6. Recommendation in summary

1. Application of target treatment (bevacizumab, cetuximab or panitumumab) to standard CT is not confirmed in the adjuvant setting.
2. Patients with stage I disease require observation without any adjuvant treatment.

3. Patients with low-risk stage II disease have some treatment options: capecitabine or 5-FU/leucovorin regimen, observation without adjuvant treatment or enrollment in a clinical trial.

4. Patients with high-risk stage II disease and poor prognostic features (T4 tumors, lymphovascular invasion, Nx lymph node status, poor differentiation bowel obstruction, positive resection margins) are considered for more aggressive adjuvant approach like 5-FU/leucovorin, capecitabine, FOLFOX, capecitabine/oxaliplatin, FLOX. This group of patients needs an observation like alternative, but there is a certain risk of disease relapse. This risk is higher without adjuvant treatment. Patients with stage III disease can receive surgical treatment followed by 6 months of adjuvant treatment with FOLFOX, capecitabine/oxaliplatin, FLOX, 5-FU/leucovorine or capecitabine only (in patients contraindicated for oxaliplatin-based chemotherapy) [6].

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