Adjuvant Chemotherapy for Colon Cancer: Evidence on Improvement in Survival

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Key Words

Colon cancer · Adjuvant chemotherapy · Fluoropyrimidines

Abstract

Clear progress has been made in the adjuvant treatment of colon cancer. Until very recently, the absolute benefit for survival obtained with the administration of 6 months' FU/LV compared with control was about 6%. Fluoropyrimidines have been shown to be at least as active and can replace intravenous FU/LV in stage III colon cancer. Based on the results of the MOSAIC and NSABP C-07 trials, the addition of oxaliplatin to FU/LV improves disease-free survival and FOLFOX for 6 months can be recommended as adjuvant treatment for patients with stage III colon cancer. The benefit of adjuvant chemotherapy in stage II disease is limited and it should be proposed in patients with high-risk features. Adjuvant treatment of colon cancer improving and the use of genetic/molecular markers with the new targeted therapies may further improve survival.

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Introduction

Colorectal cancer (CRC) accounts for 10–15% of all cancers and is the second leading cause of cancer-related death in Western countries [1]. Surgery is the primary treatment modality with curative intent in locoregion-

ally advanced colon cancer. However, 40–50% of the operated patients will relapse and require further treatment. [2]. Every year, CRC is responsible for an estimated 400,000 deaths worldwide. Clinical failure following resection of colon cancer is predominantly a result of previously undetected residual or metastatic disease. Colon cancer is not uniformly fatal and there are large differences in survival depending on the stage of disease. The pathologic stage is currently the most important determinant of prognosis. The classification systems described by the Dukes no longer fulfill the requirements of modern tumor staging. It does not take into account distant metastases, the number of lymph nodes involved or cancers limited to the submucosa. The TNM classification system is currently recommended. The updated sixth edition of the American Joint Committee on Cancer stratifies colon cancer stages II and III by use of T stage and N stage [3].

Adjuvant chemotherapy given after surgery was developed to reduce the risk of disease recurrence, either as local or distant metastases, in patients with stage II/III disease. Relapse of disease occurs in the majority of patients within the first 3 years, with the relapse rate reaching a peak in the second year [4]. The traditional endpoint of adjuvant chemotherapy studies for colon cancer has been 5-year overall survival (OS). A recent analysis of pooled data by Sargent et al. [5] from nearly 13,000 patients with stage III colon cancer found that 3-year disease-free survival (DFS) highly correlated with 5-year

Table 1. Chemotherapy regimens and dosing in adjuvant colon cancer

Regimen	Drugs and dosage	Frequency	
<i>5-FU/LV-based</i>			
Mayo Clinic	5-FU 425 mg/m ² LV 20 mg/m ²	Days 1–5 Days 1–5	q28 days
Roswell Park	5-FU 500 mg/m ² LV 500 mg/m ²	Days 1, 8, 15, 22, 29, 36 Days 1, 8, 15, 22, 29, 36	q8 weeks
LV5FU2	LV 200 mg/m ² 5-FU 400 mg/m ² bolus	Days 1, 2 Days 1, 2	q14 days
AIO	5-FU 600 mg/m ² CI 22 h LV 500 mg/m ² 5-FU 2,000 mg/m ² CI 24 h	Days 1, 2 Days 1, 8, 15, 22, 29, 36 Days 1, 8, 15, 22, 29, 36	q8 weeks
<i>Oxaliplatin-based</i>			
FOLFOX 4	OX 85 mg/m ² LV 200 mg/m ² 5-FU 400 mg/m ² bolus 5-FU 600 mg/m ² CI 22 h	Day 1 Days 1, 2 Days 1, 2 Days 1, 2	q14 days
m FOLFOX6	OX 85 mg/m ² LV 200 mg/m ² 5-FU 400 mg/m ² bolus 5-FU 2,400 mg/m ² CI 46 h	Day 1 Days 1 Days 1 Days 1–2	q14 days
FLOX	OX 85 mg/m ² LV 500 mg/m ² 5-FU 500 mg/m ²	Days 1, 15, 29 Days 1, 8, 15, 22, 29, 36 Days 1, 8, 15, 22, 29, 36	q8 weeks
XELOX	OX 130 mg/m ² CAPE 1,000 mg/m ² orally BID	Day 1 Day 1–14	q3 weeks
<i>Irinotecan-based</i>			
IFL	IRI 125 mg/m ² LV 20 mg/m ² 5-FU 500 mg/m ²	Days 1, 8, 15, 22 Days 1, 8, 15, 22 Days 1, 8, 15, 22	q6 weeks
FOLFIRI	IRI 180 mg/m ² LV 500 mg/m ² 5-FU 400 mg/m ² bolus 5-FU 2.4–3 g/m ² CI 46 h	Day 1 Days 1 Days 1 Days 1–2	q14 days
IF	IRI 180 mg/m ² LV 200 mg/m ² 5-FU 400 mg/m ² bolus 5-FU 600 mg/m ² CI 22 h	Day 1 Days 1, 2 Days 1, 2 Days 1, 2	q14 days

5-FU = 5-Fluorouracil; BID = twice daily; CAPE = capecitabine; CI = continuous infusion; IRI = irinotecan; LV = leucovorin; OX = oxaliplatin.

OS, suggesting that 3-year DFS is an appropriate primary endpoint for adjuvant chemotherapy studies. Thus, the earlier evidence of clinical and statistical benefit from chemotherapy for colon cancer may lead to earlier translation of clinical trial results into practice. In the 1980s, adjuvant 5-fluorouracil (5-FU)-based chemotherapy was proven to decrease the risk of recurrence from CRC versus observation [6–14]. Since then, many large, well-designed, randomized controlled trials have demonstrated that 5-FU modulation with leucovorin (FU/LV) offers better DFS and OS than other 5-FU mod-

ulations [15–20]; that high-dose LV is equally effective with low-dose LV; that the two most commonly administered regimens of bolus 5-FU/LV, Mayo Clinic regimen and weekly Roswell-Park regimen, have similar efficacy [19]; that there is no additional benefit to prolong treatment from 6 to 12 months [21], and that infusional regimens have similar efficacy to bolus regimens but are associated with fewer, severe toxicities [22–24] (table 1). Overall, 5-FU-based adjuvant therapies reduce the risk of recurrence by 30% and the risk of death by 26% over observation [25]. Despite this substantial reduction,

Table 2. Oral fluoropyrimidines in the adjuvant treatment of patients with colon cancer

Trial	Stage	Patients	3/5 years DFS			RFS			Survival	
			HR	p	3/5 years	HR	p	3/5 years	HR	p
X-Act ^a	III	1,987	60.6 ^a	0.87 (0.75–1.00)	61.9 ^a	0.86 (0.74–0.99)	0.04	77.6 ^a	0.84 (0.69–1.01)	0.07
FU/FA			64.2 ^a							
Capecitabine	II/III	1,608	68.3 ^b	0.79	76.4 ^b		0.52	78.7 ^b		0.88
NSABP C-06			66.9 ^b							
FU/FA			66.9 ^b							
UFT/FA										

HR = Hazard ratio; FU = fluorouracil; FA = folinic acid; NSABP = National Surgical Adjuvant Breast and Bowel Project; UFT = uracil fluorafur; DFS = disease-free survival; RFS = relapse-free survival.

^a 3 years; ^b 5 years.

many patients relapse and succumb from the disease each year, justifying the continuing effort to improve outcomes.

New Drugs

Oral Fluoropyrimidines

Several studies have investigated the activity of oral fluoropyrimidines in the adjuvant treatment of colon cancer. The X-Act study randomly assigned 1,987 patients with resected stage III colon cancer to receive either capecitabine 2,500 mg/m² daily, days 1–14 every 21 days or bolus FU/LV (Mayo Clinic regimen) for 6 months [26]. DFS at 3 years was at least equivalent to that in the 5-FU/LV group. Capecitabine improved relapse-free survival and was associated with significantly fewer adverse events than 5-FU/LV. The 3-year survival was 81.3% for capecitabine compared with 77.6% for 5-FU/LV ($p = 0.07$) (table 2).

The NSABP C-06 trial compared intravenous administration of FU/LV in Roswell Park regimen for three cycles with UFT/LV (UFT 300 mg/m²) daily and LV 90 mg daily, days 1–28, every 35 days for five cycles in 1,608 patients with stage II and III colon cancer [27]. No difference has been observed between the two treatment arms concerning 5-year DFS (66.9 vs. 68.3%) or 5-year OS (78.7 vs. 78.7%). Both regimens had similar toxicity profiles (table 2).

In a meta-analysis of three randomized Japanese studies with 5,233 patients, oral adjuvant chemotherapy (oral 5-FU, UFT, carmofur) was compared with observation [28]. Patients receiving oral fluoropyrimidine chemotherapy had better DFS (hazard ratio (HR) 0.85, $p = 0.001$) and superior OS (HR 0.89, $p = 0.04$) [28].

All these studies clearly show that the oral fluoropyrimidines are at least equally effective as intravenous bolus FU/LV in the adjuvant treatment of patients with colon cancer.

Oxaliplatin

The addition of oxaliplatin (LOHP) to FU/LV as adjuvant treatment for colon cancer has been investigated in two large randomized studies. In the Multicenter International Study of LOHP/5-FU/LV in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial, 2,246 patients with stage II and III colon cancer were randomly assigned to 6 months of treatment with LV5FU2 (de Gramont) or identical FU/LV + LOHP 85 mg/m² on day 1 of every cycle (FOLFOX-4) [29]. The primary endpoint of the study was 3-year DFS. After a median follow-up of 56.2 months, DFS was significantly higher in the FOLFOX-4 group (76.4%) compared with LV5FU2 group (69.8%). The HR was 0.77 ($p < 0.001$). For the subgroup of patients with stage III colon cancer the reduction of the relapse rate was statistically significant, with an absolute difference of 8.6% (HR 0.75). A trend but no significant difference was observed in the subgroup of patients with stage II disease, with an absolute difference of 3.5% (HR 0.82%) (table 3). Four-year survival for the whole population (both stage II and III) did not reach significance, 84.9 vs. 82.9% [30]. FOLFOX-4 was a well-tolerated schedule. The all-cause mortality in the study was 0.5% in both arms. Grade III/IV neutropenia was observed in 41% of patients receiving FOLFOX-4 compared with 5% in patients receiving LV5FU2, but infections or neutropenic fever were rare. Peripheral neuropathy was observed in 92% of the patients who received FOLFOX and in 12% was grade III. This persisted in only

Table 3. Combination chemotherapy in the adjuvant treatment of patients with colon cancer

Trial	Stage	Patients	DFS, %			
			3 years	long-term follow-up	HR	p
<i>MOSAIC</i>						
LV5FU2	II/III	2,246	72.9	69.8 ^a	0.77	<0.001
FOLFOX-4			78.2	76.4 ^a		
LV5FU2	III ^b	1,347	65.3	61.0 ^c	0.76	<0.005
FOLFOX-4			72.2	69.7 ^c		
<i>NSABP-C-07</i>						
Bolus FU/FA	II/III	2,492	71.6		0.79	0.004
FLOX			76.5			
Bolus FU/FA	III ^b	1,774	65.5		0.77	NA
FLOX			72.2			
<i>CALGB-C89803</i>						
Bolus FU/FA	III	1,260	identical		NA	0.80
IFL						
<i>ACCORD 2</i>						
LV5FU2	High-risk III	400	60		1.19	NS
IF			51			
<i>PETACC 3</i>						
LV5FU2	III	2,111	60.3		0.89	0.091
IF			63.3			
LV5FU2	II/III ^b	3,005	66.8		0.88	0.050
IF			69.6			

DFS = Disease-free survival; HR = hazard ratio; MOSAIC = Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer; LV5FU2 = leucovorin + fluorouracil de Gramont regimen; NSABP = National Surgery Adjuvant Breast and Bowel Project; FOLFOX 4 = oxaliplatin + leucovorin + fluorouracil de Gramont regimen; NA = not analyzable; CALGB = Cancer and Leukemia Group B; PETACC = Pan European Trial Adjuvant Colon Cancer; FLOX = bolus FU/FA + oxaliplatin; FA = folinic acid; IFL = FU/FA + irinotecan; IF = LV5FU2 + irinotecan.

^a Disease-free survival with median follow-up of 56.2 months.

^b Secondary endpoint.

^c Four-year disease-free survival.

1.2% for 12 months and in 0.5% for 24 months. Grade II neuropathy was seen in 4% of patients at 12 months and 3% at 24 months. Grade I neuropathy was present in 22% of patients at 12 months and 14% at 24 months, showing an improvement with time for all grades peripheral neuropathy [30].

In the NSABP C-07 study, 2,492 patients were randomly assigned to a bolus schedule of FU/LV (Roswell-Park for three cycles) versus the same FU/LV schedule + LOHP (FLOX regimen is identical to FU/LV + LOHP 85 mg/m² on days 1, 15, 29 of each cycle) [31] (table 1). The primary endpoint of the study was 3-year DFS and it was superior for patients who received FLOX compared with

FU/LV (76.5 vs. 71.6%). It corresponds to a 21% reduction in the risk of recurrence and death with the addition of LOHP. The HR for DFS was 0.79, *p* = 0.004. Survival data are not yet available. In total, 85.4% of patients who received FLOX regimen experienced peripheral neuropathy during treatment and 29.4% had symptoms 12 months later. Grade III neuropathy was noticed in 8% of patients during FLOX and 0.5% had grade III neuropathy at 12 months after stopping treatment. Gastrointestinal toxicity was relatively high, 38% of patients who received FLOX had grade III or IV diarrhea. Neutropenia occurred in 4% of patients treated with FLOX.

This NSABP trial confirms the increased activity of LOHP when added to FU/LV in the adjuvant treatment of colon cancer. But, until the results of C-07 are presented in full, it is premature to assume that FLOX and FOLFOX are interchangeable.

Irinotecan

Three trials comparing irinotecan/FU/LV with FU/LV have been reported. The United States Cancer and Leukemia Group B 89803 randomly assigned 1,264 patients with stage III colon cancer to bolus FU/LV (Roswell-Park schedule) versus the same FU/LV + irinotecan (IFL regimen) [32] (table 1). The study closed early because a higher treatment-related death rate was reported in the IFL arm. After a median follow-up of 2.6 years, no difference was observed between the two treatment groups regarding the DFS or OS. Therefore, IFL regimen cannot be considered as an option in the adjuvant treatment of patients with stage III colon cancer [33].

The French ACCORD 2 study compared LV5FU2 regimen with LV5FU2 + irinotecan (IF regimen) (tables 1, 3) [34] in 400 patients with high-risk stage III colon cancer. High-risk stage III was considered the disease presented with N2 or N1/N2 disease detected by occlusion or perforation. No improvement was observed in DFS (60% in patients treated with LV5FU2 versus 51% in patients treated with IF, HR 1.19) and the toxicity was higher for patients treated with IF.

The Pan European Trial Adjuvant Colon Cancer (PETACC)-3 trial was designed to search for an improvement in 3-year DFS, in 3,005 patients with stage II–III colon cancer, treated with irinotecan plus an infusional 5-FU schedule (AIO or FOLFIRI) [35] (tables 1, 3). This protocol defined that the occurrence of a new non-colorectal primary would be counted as an event in DFS, a definition not in accordance with most other adjuvant trials. The primary endpoint was 3-year DFS for patients with stage III disease. Secondary endpoints were DFS in the pooled stage II/III population, relapse-free survival (equal to DFS excluding second primaries non-colon cancers) in stage III patients, survival and safety. An imbalance was noted between the two arms: 17% of patients treated with LV5FU2 + irinotecan had T4 tumors, while 13% of patients treated with LV5FU2 had T4 tumors ($p = 0.006$), and that because there was no stratification for T stage. At a medium follow-up of 38 months the primary endpoint of the study was not met. Three-year DFS for stage III was 63.3% for patients treated with irinotecan compared with 60.3% for patients treated without irinotecan. The HR for 3-year DFS was 0.89, $p = 0.091$. DFS for

the pooled population (stage II and III) was borderline significant: 69.6 vs. 66.8%, HR was 0.88, $p = 0.05$. The relapse-free survival for patients with stage III colon cancer was 66 vs. 62.2% for patients with stage II. The HR for 3-year relapse-free survival was 0.86, $p = 0.045$. Patients receiving irinotecan experienced slightly higher toxicity. The 60-day mortality was $<0.5\%$ in both arms and the mortality within 30 days of the last treatment was $<1\%$ in both arms. Based on the consistent results of these trials, one can surmise that any benefit from adjuvant irinotecan appears to be of small magnitude and not likely clinically relevant when given on current FU/LV schedules.

Other Drugs

Two ongoing European trials have been designed to evaluate the addition of drugs other than LOHP or irinotecan in the adjuvant treatment of colon cancer. The Groupe Régionale d'Etudes du Cancer Colorectal (GERCOR)-03 study compares the impact of DFS on one of four containing arms: chronomodulated FU/LV with and without carboplatin or infusional FU/LV with and without carboplatin. The second study, PETACC-5, investigates whether the addition of celecoxib to FU/LV will improve DFS over placebo in 1,450 randomized patients with stage III colon cancer (table 4).

Biologics

Cetuximab is a chimeric monoclonal antibody targeting the epidermal growth factor receptor and is active in metastatic setting in patients with irinotecan refractory disease either alone or in combination with irinotecan [36]. Non-randomized phase II studies shared promising results in a first-line setting when cetuximab was combined with FOLFOX or FOLFIRI. Large studies have been designed and are ongoing in Europe and in USA in the adjuvant treatment of colon cancer evaluating FOLFOX with or without cetuximab (protocols N0147 and PETACC-8) (table 4).

Bevacizumab is a humanized monoclonal antibody that targets vascular endothelial growth factor, which is essential for tumor angiogenesis. In randomized trials for metastatic colon cancer, the addition of bevacizumab to irinotecan/FU/LV in first-line treatments or to LOHP/FU/LV in second-line treatments have shown increased activity [37]. In the adjuvant setting, two large trials are ongoing for patients with stage II/III colon cancer. The AVANT trial plans to randomize 3,450 patients with high-risk stage II and stage III colon cancer to receive FOLFOX or FOLFOX + bevacizumab or XELOX + bevacizumab (table 4). The NSABP-CO8 study plans to ran-

Table 4. Ongoing phase III trials of adjuvant therapy for colon cancer

Trial	Chemotherapy regimen	Stage	Anticipated enrollment, n	Primary endpoint
NSABP C-08	Arm 1: FOLFOX Arm 2: FOLFOX + bevacizumab	II, III	2,632	DFS
NCCTG N0147	Arm 1: FOLFOX Arm 2: FOLFOX + cetuximab	III	2,300	OS
ECOG 5202	Arm 1: FOLFOX Arm 2: FOLFOX + bevacizumab Arm 3: Observation (low-risk)	II	3,610; 1,200 high-risk	3-year DFS
GERCOR-03	Arm 1: Chromo 5-FU/LV $\pm$ carboplatin Arm 2: INF 5-FU/LV $\pm$ carboplatin	IIB, III	660–800	DFS
EORTC 40023/PETACC5	Arm 1: 5-FU/LV + 3 years' celecoxib Arm 2: 5-FU/LV + 3 years' placebo	III	1,450	DFS
AVANT	Arm 1: FOLFOX Arm 2: FOLFOX + bevacizumab Arm 3: XELOX + bevacizumab	II, III	3,450	DFS, OS
ACCORD-I	Arm 1: FOLFOX Arm 2: FOLFOX + cetuximab	III		

5-FU = 5-Fluorouracil; Chromo = chronomodulated; DFS = disease-free survival; EORTC = European Organization for Research and Treatment of Cancer; GERCOR = Groupe Régional d'Etudes du Cancer Colorectal; INF = infusional; LV = leucovorin; NCCTG = North Central Cancer Treatment Group; NSABP = National Surgery Adjuvant Breast and Bowel Project; OS = overall survival; PETACC = Pan European Treatment Adjuvant Colon Cancer.

domize 2,500 patients with resected stage II/III colon cancer between FOLFOX or FOLFOX + bevacizumab.

All these studies with cetuximab and bevacizumab in the adjuvant setting are designed to significantly improve 3-year DFS in patients with resected stage II/III colon cancer, and the oncology community anxiously awaits the results of these trials to see if the biologic agents will have the same impact on DFS and OS in the adjuvant setting as they have shown in metastatic disease.

Intraperitoneal-Intraportal Chemotherapy

Besides intravenous chemotherapy, several studies have investigated the role of chemotherapy either intraperitoneally or intraportally. Large randomized studies could not show a better outcome for patients treated with system 5-FU-based chemotherapy in combination with intraportal or intraperitoneal chemotherapy as adjuvant treatment [38].

Adjuvant Treatment for Stage II Colon Cancer

The therapeutic approach in stage II colon cancer is more controversial because of the lack of a large number of prospective randomized trials. Most of the data derive from prospectively defined subgroup analyses of trials that include stage II and stage III patients with colon cancer. The result pooled analyses as well as the Quick And Simple And Reliable (QUASAR)-1 study have attempted to answer that question [25, 39–41]. All these analyses confirm a relative risk reduction of death of 20% (12–30%) provided by adjuvant 5-FU-based chemotherapy in patients with stage II disease, but the confidence intervals are wide and do not allow definite conclusions of true benefit. In a subset analysis of the MOSAIC trial, the proportional benefit of LOHP over FU/LV and the relative risk reduction of DFS of 20% remained the same for stage II and stage III patients [42]. Whether adjuvant chemotherapy improves outcomes in stage II colon cancer patients is unlikely to ever be quantified as the number of patients needed is very high (approximately 4,000 patients per arm). However, the true absolute 5-year survival benefit from adjuvant treatment for stage II colon cancer is likely between 2 and 4% [43] and may be higher

with the newer agents. The most important ongoing clinical trial for stage II disease is ECOG 5202. This study aims to enroll 3,600 stage II patients. Tumors will be tested for loss of heterozygosity 18q and microsatellite instability. Patients with high-risk tumors (both loss of heterozygosity and microsatellite stability) will be randomized to FOLFOX or to FOFLFOX with bevacizumab. The low-risk stage II patients will be followed prospectively as an observation arm. The tumor blocks and blood from the low-risk cohort of patients will be analyzed in a translational program in order to evaluate known and possible new prognostic and predictive markers.

Future Directions

The active new drugs have led to new and more questions in the field of adjuvant chemotherapy for CRC and the answers to these questions can be given through large, well-designed, randomized trials. At the 2004 ASCO Meeting, a report correlated closely 3-year DFS with 5-year OS. Following this report, at the 2005 ASCO Meeting, the same authors announced that 2-year DFS is also tightly correlated with 5-year OS (correlation coefficient 0.74). Two-year DFS is a very attractive endpoint, but it would be premature to base studies only on this endpoint without further follow-up. If it becomes true, these surrogates will lead to more rapid reporting of adjuvant outcomes and shorten the waiting time for new effective regimens to reach the community.

Many questions regarding the selection of patients for aggressive adjuvant chemotherapy remain unanswered. Three classes of factors could be useful in clinical decision-making: stage-independent prognostic factors, factors that can predict response to treatment and factors that can predict toxicity to various agents. Stage-independent prognostic factors could be used to distinguish a group of patients at higher risk than similarly staged patients, so that they receive more aggressive treatment. ECOG 5202 trial uses 18qLOH (loss of heterozygosity) and MSS (microsatellite stability) as bad prognostic factors. In patients with stage II colon cancer, 18qLOH carries risk of recurrence that is more akin to patients with stage III at presentation [44]. Microsatellite instability (MSI) carries a lesser risk of later metastatic recurrence that does an MSS tumor phenotype [45]. Factors that can predict response to treatment could help select which treatment option is most likely to be beneficial. MSI is considered to be a predictor of response to 5-FU-based adjuvant chemotherapy, as it results from some retro-

spective analyses but not by others [46–48]. Prospective studies are needed to confirm the ability of high MSI expression in predicting response to 5-FU-based chemotherapy. Another factor that could be useful in predicting 5-FU response is high thymidylate synthase (TS) expression, which correlates with low chance of response to 5-FU, as results retrospectively from many studies. The expression of TS may not be of great clinical utility, because 5-FU may be a requirement for LOHP efficacy and not dispensable even in high TS patients. Pharmacogenomics predict toxicity by testing for common genetic polymorphism in the 5-FU-inactivating enzyme dihydropyrimidine dehydrogenase (DPD), activity and severe, potentially lethal, 5-FU toxicity. A cheap and easily reproducible method for testing for this abnormality is sought after, so that 5-FU alternatives might be chosen in patients with very low DPD activity. Another useful predictor of toxicity is polymorphism of the UGT1A1 gene, which is responsible for glucuronidation and thus inactivation of SN-38, the active metabolite of irinotecan, and predicts for severe neutropenia in irinotecan administration [49].

Summary and Conclusion

The 1980s introduced clinical trials that showed for the first time the effectiveness of adjuvant chemotherapy for patients with resected stage III colon cancer. Since the establishment of 5-FU + levamisole in adjuvant treatment, many large randomized trials have modified adjuvant chemotherapy, showing that: 6 months of 5-FU/LV is equivalent to 1 year of 5-FU/levamisole; weekly schedules of 5-FU/LV are equivalent to the monthly schedule; levamisole is not necessary in the adjuvant therapy; the high-dose 5-FU/LV is equivalent to the low dose with different toxicity profiles, and infusional 5-FU schedules are equivalent to bolus 5-FU schedules with less toxicity. In more recent studies, oral fluoropyrimidines (UFT and capecitabine) are proven to be of equal efficacy with bolus 5-FU/LV, IFL is more toxic and not superior to bolus 5-FU/LV. Pending data will determine the efficacy of FOLFIRI compared to 5-FU/LV. Combinations of oral agents with LOHP are being studied and trials that have incorporated the new monoclonal antibodies cetuximab and bevacizumab are ongoing. Current strategies in investigation of the effects of adjuvant chemotherapy include prospective analysis of prognostic and predictive markers of risk and response.

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