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Adjuvant treatment of colon cancer – past, present and future

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INTRODUCTION

Colorectal cancer is common in economically developed countries, particularly in Europe, North America and Australia and is one of the leading causes of cancer-related deaths in the Western world. Every year, colorectal cancer is responsible for an estimated 400.000 deaths worldwide. Approximately 60.000 people die from colorectal adenocarcinoma among the 150.000 new cases which are diagnosed in Europe each year.

Seventy % of patients with colorectal cancer present with apparently localized disease. In these patients surgery can be curative, but up to 50% of patients who undergo a complete resection will relapse and ultimately die of metastatic disease. Adjuvant chemotherapy has been developed to reduce the incidence of relapse and death. Given the high incidence of colorectal cancer an adjuvant treatment that will lead to an only relatively small increase in survival will have a large impact on the absolute number of deaths in this disease.

Table 1. Prognosis of colorectal cancer in relation to staging

UICC-stage	TNM classification	5-year survival (%)
Stage I	pT1N0M 0	> 90
	pT2N0M 0	
Stage II	pT3N0M 0	70
	pT4N0M 0	50
Stage III	$pT_{any}N+M$ 0	30-50
IIIa	$pT_{1-2}N1M$ 0	
IIIb	$pT_{3-4}N1M$ 0	
IIIc	$pT_{any}N2M$ 0	
Stage IV	$pT_{any}N_{any}M+$	< 5

Colorectal cancer is not uniformly fatal and there are large differences in survival depending on the stage of the disease. The pathologic stage is currently the most important determinant of prognosis. The classification system described by Dukes in 1930 is still widely used. However, the original Dukes' system no longer fulfills the requirements of modern tumor staging, as it fails to take into account distant metastases, the number of lymph nodes involved, and carcinomas limited to the submucosa. Therefore the TNM classification of the American Joint Committee on Cancer (AJCC) is currently recommended for daily routine and in clinical trials. The prognosis depends on the stage at which the tumor is diagnosed. In patients with a stage I tumor (pT1 or pT2N0M0), the 5-year survival exceeds 90%. In patients with a stage II tumor, (pT3 or pT4N0M0) (Dukes B), the survival is variable. In patients with a pT3N0M0 tumor, the 5-year survival is approximately 70%, while in those with a pT4N0M0 tumor, the 5-year survival is only around 50%. One of the most important prognostic factors in stage II colon cancer is the number of lymph nodes analyzed. Twelve lymph nodes are required in UICC recommendation. In patients with stage III tumors ($pT_{any}N+M0$) (Dukes C), the 5-year survival is 30%-50%. In patients with metastatic colorectal cancer (stage IV), the 5-year survival is < 5% (Table 1).

THE PAST

STAGE III

There is a general consensus that adjuvant treatment is indicated in stage III colon cancer. Different regimens of 5-fluorouracil (5-FU)/ folinic acid (FA = leucovorin) were utilized. Until a few years ago the Mayo Clinic regimen (5 days/every 4 weeks) and the Roswell Park regimen (weekly for 6 consecutive weeks followed by 2 weeks of rest) were considered to be standard options.

The Intergroup trial (INT-0035) was the first large-scale study to demonstrate the significant effect of a postoperative adjuvant treatment in patients with stage III colon cancer. This trial randomised 1.296 patients with stage II and III cancer (929 with stage III cancer) to one of the three arms: (a) surgery alone, (b) surgery plus 12 months of levamisole, or (c) surgery plus 12 months of 5-FU plus levamisole. The study showed a 15% absolute reduction (± 40% relative reduction) in risk of recurrence and a 16% absolute reduction (33% relative reduction) in overall death rate (3.5 year survival 47% vs 63%) with a combination of surgery plus 5-FU/levamisole in patients with stage III colon cancer (1,2).

The evidence that adjuvant therapy is effective in colon cancer was further confirmed by two controlled studies that compared 5-fluorouracil/leucovorin (5-FU/LV) treatment for 6 (3) or 12 months (4) and by a Dutch trial that compared 5-FU + levamisole with control (5). In addition, the pooled 6-month results of three trials of 5-FU/LV showed significant increases in 3-year event-free and overall survival (22% relative risk reduction in mortality) in comparison with a control (6).

The NSABP (National Surgical Adjuvant Breast and Bowel project) protocol C-03 indicated a disease free (73% versus 64%) and overall (84% versus 77%) survival advantage for the 5-FU/FA combination when compared with MOF (methyl-CCNU, oncovin, 5-FU) at 3 years for patients with Dukes' stage B and C colon cancer (7).

The results of three large adjuvant American trials in which several thousands of patients have been treated provided additional data. In a large, randomized study by the North Central Cancer Treatment Group (NCCTG) and the National Cancer Institute of Canada (NCIC), it was shown that there was no additional benefit associated with administration of a full year of chemotherapy compared with just 6 months of treatment with the same regimen. In the same study, it is shown that, if only 6 months of chemotherapy was administered, patient survival was significantly inferior with the 5-FU plus levamisole regimen compared with the 3-drug regimen of 5-FU plus levamisole plus leucovorin (8). The Intergroup reported that there was no additional benefit from the addition of levamisole when 5-FU/FA is given, and moreover 6-8 months of treatment with 5-FU/FA was as efficient as 12 months of 5-FU/levamisole (INT-0089) (9). The NSABP C-04 study showed similar results for 1 year of

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treatment with 5-FU/levamisole, 5-FU/FA and 5-FU/FA/levamisole (10). 5-Year DFS rates with FU/FA in these trials ranged from 57%-65%. A very large study was the QUASAR (Quick And Simple And Reliable) trial by the United Kingdom Coordinating Committee on Cancer research (UKCCCR) that confirmed that there was no difference between weekly and monthly FU/FA and that low dose of FA was as effective as high dose (11).

Taking into account the increased toxicity of the 3-drug combination (5-FU/FA/levamisole) compared with the combination of 5-FU/FA, treatment with iv bolus 5-FU/FA for 6-8 months has been the standard or reference treatment for Dukes' C (stage III) colon carcinoma for more than a decade (12). Other treatment modalities such as active immunotherapy, the use of antibody 17-1A (Panorex) and portal vein infusion have all been abandoned because of negative outcome of conducted trials (12).

Infusional FU

Because it has been shown that infusional 5-FU ± FA regimens are more efficient in terms of response rate and time to tumor progression (TTP) and better tolerated than bolus 5-FU ± FA regimens in patients with advanced colorectal cancer (13-17), several studies evaluated the role of infusional 5-FU regimens in the adjuvant treatment: The South West Oncology Group (SWOG) study 9415/INT-0153 evaluated protracted continuous infusion (PCI) of 5-FU (250 mg/m^2 for 9 weeks x 3) + levamisole versus Mayo regimen + levamisole in stage C and high-risk stage B colon cancer. With 1078 randomized patients there were no survival differences at 3 years (18). A study from the UK compared PCI of 5-FU (300 mg/m^2 for 12 weeks) with Mayo regimen for 6 months and found similar results (19). A French randomized trial conducted by the GERCOR (Oncology Multidisciplinary Research Group) compared 6 or 9 months of treatment with an infusional FU/FA regimen (FA 200 mg /m^2, 2 hour infusion followed by FU 400 mg/m^2 as a bolus and 600 mg/m^2 as a 22 hour infusion for 2 consecutive days [LV5FU2] every 2 weeks) with a monthly bolus regimen in patients with stage II and III colon cancer. The infusional regimen was better tolerated and resulted in equivalent efficacy,

DFS of 73% at 4 years for both regimens (20). The conclusion of these trials is that, in the adjuvant setting, infusional regimens are better tolerated with equivalent activity. Results of the completed PETACC (Pan European Trials in Adjuvant Colon Cancer)-2 trial were presented at the ASCO meeting this year and led to the same conclusion (21). It is important to realize that infusional regimens can be better combined with new drugs (see below).

Oral fluoropyrimidines

The oral fluoropyrimidines, capecitabine and uracil/ftorafur (UFT) + FA, have also been evaluated in the adjuvant treatment of colon cancer. In the study named X-ACT (XELODA in Adjuvant Colon Cancer Therapy), capecitabine (Xeloda) was compared with Mayo regimen in patients with stage III colon cancer. Capecitabine yielded superior tolerance and comparable efficacy (22). Similarly in NSABP-06 protocol, UFT/LV yielded the same results as weekly bolus 5-FU/FA in a mixed population of stage II/III patients, 5-year survival 78.7% in both arms (23). These data show that the oral drugs can be used instead of bolus FU/FA regimens. Whether the oral fluoropyrimidins are equal to infusional FU/FA regimens is unknown, because no direct comparisons have been made. In indirect comparisons, however, infusional 5-FU appears to be more active and less toxic than capecitabine (24).

STAGE II

Many patients with stage II colon cancer currently receive chemotherapy, although firm data from prospective randomized trials in stage II disease are lacking. Several phase III trials included mixed populations of stage II and III patients and conclusions for stage II patients were derived from retrospective subgroup analyses.

In the INT 0035 trial for stage II the 3.5-year RFS was 77% in the surgery arm and 84% in the adjuvant arm, a non-significant difference. In the IMPACT B2 group the 5-year DFS was 73% with surgery only versus 76% with adjuvant 5-FU/FA and overall survival 80% and 82% respectively (25). In the QUASAR trial weekly FU/FA resulted in a decreased 5-year recurrence rate (22% vs. 26%) with an absolute survival benefit of 2.9% over surgery alone. Because of the large number of patients included this difference was significant (26), but the clinical relevance of such a small benefit may be questioned.

The NSABP group, after combining data from four of the group's trials including stage B and C colon cancer patients, reported that all patients with Dukes' B colon cancer likely benefit from adjuvant chemotherapy. The relative reduction in mortality, recurrence or disease-free survival was, in most instances of the NSABP trials, as great for Dukes' B patients as for Dukes' C patients. The relative mortality reduction was 30% for Dukes' B patients and this occurred irrespective of the presence or absence of adverse prognostic factors (27). These conclusions were however, criticized based on the retrospective nature of the data and because of the fact that different regimens (including portal vein infusion) and different control arms were put together (28).

Thus, it appears reasonable to state that 70%-77% of stage II patients are cured with surgery alone at 3.5-5 years and only an additional 3%-8% may benefit from adjuvant FU/FA. It is possible that this small benefit is mainly derived from stage II patients with a "high-risk" or from false stage II patients i.e. stage III patients who have been understaged because too few nodes were retrieved or examined.

There is, however, no common definition of a high-risk stage II colon cancer population. Several factors may be important: T_4 tumor, poor tumor differentiation, less than 10 nodes examined, perineural invasion, venous invasion, lymphatic vessel invasion, tumor soiling or perforation and colonic obstruction at presentation. Based on available prospective data however, it is difficult to define a high-risk population that certainly benefits substantially from an adjuvant treatment.

Molecular markers are important and data are emerging on their prognostic value. Treatment decisions, however, can currently not be based on these molecular markers. The most relevant molecular markers at present appear to be microsatellite instability (MSI), 18q-LOH (allelic loss in chromosome 18) and thymidylate synthase (TS) expression.

Future trials should therefore focus on the demonstration of a benefit of chemotherapy in stage II colon cancer, on the selection of patients at high risk and on the demonstration of the value of clinical, pathologic and molecular predictive markers for recurrence.

THE PRESENT

The topoisomerase I inhibitor irinotecan (CPT-11) and the diaminocyclohexane platinum derivative, oxaliplatin, are two drugs that have established activity in advanced colon cancer. Therefore these agents should be potentially effective in the adjuvant setting. Large phase III trials have been conducted to evaluate the role of irinotecan and of oxaliplatin in combination with 5-FU/FA in the adjuvant treatment of stage II and III colon cancer.

Irinotecan + 5-FU/FA

In CALGB (Cancer and Leukemia Group B) trial C89803 bolus FU/FA + irinotecan (IFL) w as compared with FU/FA alone. A total of 1265 stage III patients were randomized. At a median follow-up of 3 years there were no significant differences in DFS or overall survival but the IFL regimen was more toxic with 18 vs 6 early deaths (p=0.008). The conclusion was that IFL should not be used in adjuvant treatment (29).

Because infusional FU/FA has a superior therapeutic index, the combination of infusional FU/FA (weekly 24h infusion or biweekly LV5FU2) or infusional FU/FA + irinotecan (weekly 80 mg/sqm or biweekly 180 mg/sqm : FUFIRI or FOLFIRI) was assessed in Aventis V307 (stage II/III)/PETACC 03 (stage III only) trial. A total of 3.278 patients (stage II/III: 945/2333) were randomized. Of the stage III patients 2.094 were treated with LV5FU2 ± irinotecan. Median follow-up was 32 months. The primary endpoint for PETACC-3 was DFS at 3 years. There were no significant differences between the two

regimens (absolute difference of 3% in favor of FOLFIRI, p=0.091) regarding the primary endpoint. Mixing the two populations together and substituting RFS for DFS a significant difference was observed. Correcting retrospectively for T status, a significant difference in 3 year DFS also became apparent (30). These analyses however were criticized at the 2005 ASCO meeting. Most investigators would consider results of PETACC-3 sofar as negative in its primary endpoint. PETACC-3 failed to prove activity of irinotecan in the adjuvant setting.

Lastly the FOLFIRI regimen has been assessed in high-risk stage III colon cancer in comparison with LV5FU only. High risk was defined as N2 (3+ nodes) or N1 plus additional risk factors such as occlusion or perforation. A total of 400 patients were entered. DFS at 3 years was 60% in the control arm compared with 51% in the combination arm. Adjusting for the observed imbalances in T stage and number of affected lymphnodes did not change these results. The conclusion was that the study failed to demonstrate an improvement in DFS in patients with high-risk stage III colon cancer (31).

Oxaliplatin and 5-FU/FA

In concert with infusional 5-FU/FA in combination with irinotecan, oxaliplatin was assessed in combination chemotherapy in the adjuvant setting. Results of the Multicenter International Study for Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) became available in 2003. This study included 2246 patients with stage II (40%) and stage III (60%) patients, who were randomized to either LV5FU2 infusion alone or plus oxaliplatin 85 mg/sqm (FOLFOX-4). The 3-year DFS was 78.2% in the FOLFOX group compared to72.9% in the control group (p= 0.002) (32).

Table 2. Disease-free survival (DFS) at 3 and 4 years in patients with stage II or III colon cancer randomized to treatment in MOSAIC

Parameter	FOLFOX 4	LV5FU2
Total population	n=1123	n=1123
3-year DFS	78.2%	72.9%
4-year DFS	75.9%	69.1%
HR 0.76 (0.65-0.90)		
Stage III patients	n=672	n=675
3-year DFS	73.0%	65.7%
4-year DFS	69.7%	61.0%
HR 0.75 (0.62-0.90)		
Stage II patients	n=451	n=448
3-year DFS	87.4%	84.5%
4-year DFS	85.1%	81.3%
HR 0.80 (0.58-1.11)		

In table 2 the DFS rates at 3 and 4 years in the total population and in subgroups is displayed. There was a significant 24% reduction in recurrence risk for the entire population and for patients with stage III. The differences in treatment outcome were notable in most subgroups, 5.4 % in high-risk stage II (defined as T4 and/or bowel obstruction and/or perforation and/or poor differentiation and/or venous invasion and/or < 10 nodes examined), 7% in patients with stage III N1 and 11% in patients with stage III N2. The 5-year survival curves sofar were identical, but prolonged follow-up is needed. Toxicities with FOLFOX-4 included neutropenia, diarrhea, vomiting and grade 3 neuropathy that resolved in the majority of patients (12.4%) during treatment that decreased to 1.1% at 1 year of follow-up. The toxic death rate was 0.5% in both arms. Based on these results, the FOLFOX regimen has worldwide been adopted as the new standard of care.

Finally in protocol C-07 NSABP assessed oxaliplatin in combination with bolus 5-FU/FA. Patients with stage II and III colon cancer were randomly assigned to weekly bolus 5FU/FA for 6 weeks in each 8 weeks cycle x 3, or to the same plus oxaliplatin, 85 mg/sqm on weeks 1,3 and 5 of each 8 week cycle x 3 (FLOX). Results in 2407 patients were comparable to the outcome of MOSAIC. The 3-year DFS was 76.5% in the FLOX arm vs 71.6% in the control arm. Eight percent of patients had grade 3 neurotoxicity with FLOX which dropped to 0.5 % after cessation of chemotherapy. This lower incidence was probably related to the lower cumulative dose of oxaliplatin in FLOX as compared to FOLFOX. The incidence of grade 3-4 neutropenia was only 4%, but severe diarrhea occurred in 38% and 56 patients treated with FLOX had to be hospitalized because of severe diarrhea and dehydration as opposed to 34 treated with FU/FA. There were 14 and 15 deaths during treatment with FU/FA and FLOX (33).

THE FUTURE

Now that infusional FU/FA/oxaliplatin is the accepted new standard therapy in stage III colon cancer and possibly in high-risk stage II, the next generation of trials will use this regimen as a control arm. Is FOLFOX-4 the ideal regimen or should FOLFOX-6 or FOLFOX-7 be preferred? In these latter protocols the dose-intensity of 5-FU is higher and in FOLFOX-7 bolus 5-FU, which probably adds nothing but toxicity, is no longer utilized. Another question is whether oral 5-FU such as capecitabine can replace infusional 5-FU/FA. Ongoing or completed trials in advanced disease will certainly provide an answer. Capecitabine combined with oxaliplatin will also be assessed in the adjuvant setting. Results of a trial from Mayo clinic (N016968) comparing bolus 5-FU/LV with capecitabine + oxaliplatin (XELOX) will become available soon as well as the results of a German trial with the same design.

Besides chemotoxic drugs, molecular target agents such as the epidermal growth factor receptor inhibitor cetuximab and the vascular endothelial growth factor inhibitor bevacuzimab will be assessed. These agents have shown to improve therapeutic outcome in advanced disease when added to chemotherapy (34,35).

NSABP will assess in protocol C-08 FOLFOX ± bevacuzimab, while in Intergroup N0147 FOLFOX will be compared to FOLFOX + cetuximab. In the AVANT study more that 3.000 patients with high-risk stage II and III will be recruited who will be randomized to a) FOLFOX-4, b) FOLFOX + bevacuzimab, followed by bevacuzimab alone and c) XELOX + bevacuzimab followed by bevacuzimab.

Finally in PETACC-8 FOLFOX ± cetuximab will be assessed. In table 3 a summary of important new trials is shown.

Table 3. Selection of planned/ongoing large scale cooperative trials

Group/Acronym	Stage	Study protocol
ECOG 5202	II	High risk FOLFOX ± bevacuzimab
		Low risk : observation
NSABP C-08	High-risk II and III	FOLFOX-6± bevacuzimab
INT 0147	High-risk II and III	FOLFOX-6 ± cetuximab
AVANT	High-risk II and III	FOLFOX-4 ± bevacuzimab
		vs XELOX + bevacuzimab
PETACC 8	III	FOLFOX-4 ± cetuximab

DISCUSSION

The adjuvant treatment of colon cancer remains a complex and confusing area (36). Several important questions need further discussion. Why are the oxaliplatin trials positive and the irinotecan studies not? In advanced disease both drugs appear to have similar activity and a survival benefit was observed in two

large studies assessing irinotecan in combination with FU/FA versus FA alone (reported by Salz and by Douillart in 2000). On the contrary in two studies that compared oxaliplatin combination with FU/FA no significant survival benefit was observed (reported by Giachetti and by De Gramont in 2000). Two factors that might explain the apparent higher activity of oxaliplatin are that time to response with oxaliplatin combination appears to be shorter and with oxaliplatin combination more often downstaging of livermetastases leading to resectabilty appears to happen. Anyway, also taking into account the controversy in the interpretation of these data, a longer follow-up of PETACC-3 is needed before irinotecan should be definitively discarded in the adjuvant setting.

The 3-year DFS has now been accepted as a primary endpoint in adjuvant studies because it predicts overall survival at least in studies that utilize 5-FU/FA (37). The FOLFOX regimen has been accepted based on the positive outcome in its primary endpoint : DFS. It remains to be seen whether this holds true when more potent agents are utilized. Patients who relapse after FOLFOX or FOLFIRI might do less in the metastatic setting because less active drugs are available.

Although 3-year DFS appears to be an acceptable endpoint in itself, overall survival after 5 years remains important and should be reported in all new studies. Overall survival must remain the ultimate standard endpoint which accounts for the complete impact of the choice of adjuvant therapy on long-term outcome (38). A further point is that there should be agreement on the exact definition of endpoints, be it disease-free survival or relapse-free survival (excluding second primaries).

Finally the most important question as asked by Douillard in a nice editorial (36) remains: who benefits from what? It should be realized that overall in stage III 40%-50% of patients are cured by surgery. An additional 15% will benefit from adjuvant chemotherapy with FU/FA and an additional of 8% from FOLFOX. In stage II the benefits are smaller and 70% will be cured by surgery only, 8% will benefit from FU/FA and an additional 3%-4% from FOLFOX.

In table 4 an estimate of 5-year DFS according to stage and treatment is provided. It appears clear that in the more advanced stages the indication for adjuvant therapy is more compelling (i.e. T4 with N+ certainly must receive adjuvant therapy). In stage IIIc for instance the benefit in 4-year DFS of FOLFOX is an additional 11% as opposed to 8% for the overall stage III population. Many patients however still receive unnecessary adjuvant chemotherapy and it is clear that there is an urgent need for the identification of predictive and prognostic factors for individual patients.

Table 4. Estimated 5-year DFS rate according to stage, grade of differentiation and adjuvant chemotherapy with FU/FA

Nodal Status	T stage Low grade			High grade	
		Surgery	+AC	Surgery	+AC
0 nodes	3	74	82	70	79
	4	63	74	57	70
1-4 nodes	1-2	71	81	67	77
	3	53	66	46	61
	4	37	53	30	46
≥ 5 nodes	1-2	51	64	44	59
	3	27	44	21	37
	4	13	27	9	21

AC: adjuvant chemotherapy with FU/FA
After GILL et all. ASCO 2003, JCO 2004

Some prognostic markers have been identified such as MSI and 18q-LOH but the value of these factors still have to be demonstrated prospectively. Some ongoing trials will hopefully provide more information. Investigators are discussing the item of individualized treatment based on well established factors now for nearly 10 years, but sofar no convincing data have been produced.

When targeted therapies will provide small additional benefits in adjuvant setting the field will even become more complex. The primary goal for oncologists should be the definition of better treatment indication parameters, so that patients who do not need it can avoid toxic therapy. The question however can be raised whether such universal and reliable parameters really exist. For the moment a completely individualized and tailored therapy remains a quite futuristic perspective.

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