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In Europe at least 60 000 patients with resectable colon cancer die every year from their disease. Soon after the development of 5-fluorouracil (5-FU) and from the beginning of the early 1950s, clinical trials have been performed to improve the cure rate of these patients by the use of adjuvant chemotherapy. A recent meta-analysis analysed the results of 12 079 patients treated within 29 prospective randomised trials reported from 1953 to 1993 with 5-FU-based adjuvant chemotherapy. Despite the large heterogeneity in terms of patient selection, prognostic factors, as well as schedule and dose of chemotherapy, a small but significant survival benefit was detected with an odds ratio of 0.81 (95% confidence interval (CI) 0.69–0.94), which implies an increase of 5% in survival with chemotherapy [1]. The more recent studies performed according to proper methodology and active chemotherapy (either 5-FU plus levamisol or 5-FU plus folinic acid) have unanimously proven that adjuvant chemotherapy is effective and increases the 5-year survival rate by 10–15%.

This means that 1–2 out of every 10 patients with high risk stage II or stage III colon carcinoma is cured by adjuvant chemotherapy. This translates to a reduction in mortality of 22–33% [2, 3]. Although this relatively low figure seems to indicate a relatively small benefit and at least 85% of the patients undergoing adjuvant chemotherapy are treated without any beneficial effect, the absolute benefit in terms of the number of cured patients worldwide is very high (at least 7,000–8,000 per year in Europe), due to the high number of patients with high risk stage II and III colon cancer. Altogether, there is overwhelming evidence that adjuvant chemotherapy should be regarded as standard in patients with resected high risk colon cancer.

Therefore, the authors of the 'pro' (pp. 1652–1655) paper as well as 'contra' (pp. 1655–1659) paper are stating a clear 'pro' for the use of adjuvant chemotherapy in all patients with high risk stage II and III colon cancer. For most colleagues this statement seems to be unnecessary in 1998, but as stated by Rougier ''many physicians, especially in Europe, are not convinced of the value of adjuvant chemotherapy'' and are still not. This is indicated by the fact that recently in The Netherlands a prospective trial in stage III colon cancer was performed which contained a control arm with surgery alone, and a current trial conducted by surgeons in Germany also contains an untreated control arm. The main reason for these studies, mainly driven by surgical colleagues, was that the quality of surgery, for example in the American Intergroup Trial, was questioned, leading to an unusually low 5-year survival of 50% in the control arm. Although the quality of surgery is indeed very heterogeneous and the risk of relapse, perhaps also survival, can, among other factors, also depend on the type and quality of the surgery performed, this applies to the control as well as the experimental arm of these studies. Table 1 compares the overall survival rate for untreated controls and adjuvant chemotherapy in stage III colon cancer from the American Intergroup Trial and the Impact Study [2, 4]; independent of the outcome of the control group, which is somewhat different in that there is a 55% 3-year survival in the Intergroup Study and a 64% 3-year survival in the Impact Study, the reduction in mortality with adjuvant chemotherapy is 33% in both studies with either 1 year 5-FU/levamisol in the American Intergroup Study or 1 year 5-FU/folinic acid in the European Impact Study. This indicates that independent of the quality of surgery, the effect of adjuvant chemotherapy is real. It is, however, unclear as to what extent 'optimal' surgery could further reduce the mortality beyond the effect of adjuvant chemotherapy: a topic which has not been explored in the articles by Slevin and Papamichael and Rougier. It must clearly be stated that the best surgery for colon cancer is required for every patient as the basis for any adjuvant treatment. Therefore, patients should only be operated upon by experienced surgeons who undergo some type of quality control.

However, due to the sincere hesitation of many members of the scientific community as well as doctors, to follow the guidelines of the NIH consensus conference for the use of adjuvant chemotherapy, in several European countries only a proportion of patients with high risk stage II and stage III colon cancer is treated by adjuvant chemotherapy, probably as low as 50% in some countries. Therefore, it cannot be stated often enough that adjuvant chemotherapy should be the standard in high risk resected colon cancer.

Which protocol is the standard?

What then is the standard treatment protocol for adjuvant chemotherapy? Again there is no 'contra'; both authors agree that treatment should be either 6 months of 5-FU/folinic acid or 12 months of 5-FU/levamisol. Although there is no difference in relapsed free and overall survival between these different regimens, they clearly differ in toxicity. As shown in the recent US Intergroup Study (Table 2), 5-FU/levamisol is associated with significantly less grade 3/4 stomatitis and diarrhoea and also somewhat less bone marrow toxicity than 5-FU/folinic acid given over 5 days every 4 weeks. However, 5-FU/levamisol must be given for 12 months instead of 6 months for the 5-FU/folinic acid regimen. This indicates that a choice between more toxicity for half the duration, or less toxicity for double the treatment duration, exists. The protocol of weekly 5-FU/high dose folinic acid (6 months' duration) has shown even less bone marrow toxicity than 5-FU/levamisol and nearly no grade 3/4 stomatitis, but is associated with 30% grade 3/4 diarrhoea. Therefore, as stated by Rougier, there is no one standard adjuvant chemotherapy, but several standards which should be chosen on the basis of toxicity, treatment burden and cost, as well as individual patient needs.

The combination of 5-FU/folinic acid/levamisol is the most toxic and the most costly protocol; even if the result of the Intergroup Study 0089 revealed a small or even a significant survival benefit for this combination it should be questioned whether this combination could be a standard out of clinical trials. A current trial of the NCCTG and NCIC is investigating this combination of 5-FU/folinic acid plus levamisol in standard dose versus high doses of levamisol, since

Table 1. *Comparison of* 3*-year relapse free and overall survival in stage III colon carcinoma in the Intergroup study* [4] *and the impact study* [2]

	Intergroup study 5-FU/levamisol (12 months)	Impact study 5-FU/folinic acid (12 months)
No. of patients	619	652
Relapse free survival at 3 years		
Control	47%	44%
Chemotherapy	63%	62%
Overall survival at 3 years		
Control	55%	64%
Chemotherapy	71%	76%
Reduction of mortality	33%	33%

5-FU, 5-fluorouracil.

Table 2. *WHO grade III/ IV toxicity with different protocols for adjuvant chemotherapy in stage III colorectal cancer* [5]

	5-FU/ levamisol %	5-FU/FA low-dose days 1–5 every 4 weeks %	5-FU/FA high-dose weekly %	5-FU/FA + levamisol %
Leucopenia	9	12	3	15
Granulocytopenia	19	24	4	35
Stomatitis	3.6	18	1.4	22.6
Diarrhoea	11.4	21	30	18

5-FU, 5-fluorouracil; FA, folinic acid.

preclinical data have demonstrated a clear dose-dependent enhancement of 5-FU cytotoxicity in colon cancer cell lines by levamisol.

Relevance of dose intensity

The topic of dose intensity and outcome of adjuvant treatment has not been mentioned by either of the authors. It should be clear that all mentioned protocols are based on bolus 5-FU, this means an injection which should not last more than 3 min. A prolongation of this injection, e.g. a 2 h infusion, will result in less efficacy as demonstrated in patients with advanced colorectal carcinoma by the Scandinavian group [6]. Furthermore, within the reported adjuvant chemotherapy trials, the doses actually given are far from ideal; in the Intergroup Study with 1 year treatment of 5-FU/levamisol approximately 30% of the patients stopped treatment early due to toxicity and in the recently reported NCCTG trial with 6 months' treatment of 5-FU/folinic acid, according to the Mayo Clinic regimen, only 1/3 of the patients received $\geq 80\%$ of the target dose of 5-FU in cycles 4 to 6 [3]. It is presently completely unclear whether a dose reduction of that amount has led to a poorer outcome and whether dose intensity is important for this type of adjuvant chemotherapy. This topic, even though not discussed in either paper, is of major relevance in clinical practice.

Adjuvant chemotherapy in stage II?

The proportion of patients with stage II varies from 0 (Intergroup Study) to 56% (Impact Study) and also all current studies include patients with stage II and high risk criteria into clinical trials. However, two separate analyses for patients with stage II revealed no significant survival benefit for stage II as a whole. However, the sequential NSAPB studies have demonstrated that the gain in survival was of the same magnitude for stage II as for stage III. This has also been demonstrated by a meta-analysis of three combined studies [7], although the absolute difference in survival (2%) is extremely small.

Prognostic factors for relapse

However, despite the congruent statement of both authors that adjuvant chemotherapy should also be offered to patients with high risk stage II colon cancer (stage B_2 according to the Dukes' classification with obstruction or perforation with serosa infiltration), this question is far from being answered. Therefore, the statement from Rougier that ''patients should be treated within clinical trials'' should be very much supported. The reason is clear: do we really know which patient should be treated and will have real benefit from adjuvant chemotherapy? There is now a solid basis of data indicating a whole bunch of prognostic factors, which have been derived

Table 3. Markers in sera and tumour tissue with prognostic value in stage II and III colorectal cancer

Markers indicating	Proven prognostic factor		References
	Univariate	Multivariate	
1. Higher stage than by classical pathological means			
Cytokeratine staining in liver	+	–	[8]
Cytokeratine immunohistological staining	+	–	[9]
K-ras expression	+	–	[10]
2. More aggressive biology			
CEA in sera	+	+	[11]
p185/neu overexpression	+	+	[12]
Ki-ras mutation	+	+/–	[13]
Mutation *DCC*/LOH 18q	+	+	[14, 15]
3. Increased proliferation			
Aneuploidy	+	+/–	[16, 17]
High DNA index	+	+	[17, 18]
Proliferation cell nuclear antigen expression	+	+	[19, 20]
p27 Kip 1 overexpression	+	+	[21]
4. Less differentiation			
Decreased level of sucrase-isomaltase	+	+	[22, 23]
5. Increased migration adhesion invasion			
E-cadherin downregulation	+	+	[24]
CD44 variant 6 expression	+	–	[25–27]
High vascular endothelial growth factor expression	+	+/–	
6. Decreased apoptotic capacity			
p53 mutation/LOH 17q	+	+	[28]
bcl-2 overexpression	+	+/–	[29]
Disturbed signal transduction of CD 95 receptor (Fas)	+	–	[30]
7. Immune function			
NK cell infiltration	+	+	[31]
CD95 ligand (fas-l) expression (induction of T-cell apoptosis)	+	–	[30]
8. Miscellaneous			
Low IGF-I receptor/high prolectin (ratio)	+	–	[32]
9. Level of chemotherapy resistance			
Thymidylate synthase overexpression	+	+/–	[33–37]

LOH, loss of heterozygosity; CEA, carcinoembryonic antigen; NK cell, natural killer cell; IGF-I, insulin-like growth factor I.

from molecular investigations of the tumour tissue and which are highly potent in predicting the biological behaviour of the tumour and the prognosis of an individual (Table 3). Beyond more accurate lymph node staging, these factors constitute indicators of higher WHO stage, proliferative activity, biological aggressiveness, apoptotic capacity, migration, adhesion and invasion capacity as well as immune functions. Most of these factors have been demonstrated to be independent predictors of relapse and survival, but these data derive from retrospective analyses of subcohorts of patients and are not proven in prospective clinical trials. In particular, since all these data have been derived from patients without adjuvant chemotherapy, it is completely unknown what impact adjuvant chemotherapy could have on the prognostic value of these factors. Table 4 gives some examples of how important these factors are in predicting survival within stage III as well as in stage II. For example in the study of Pricolo and colleagues [28] patients with a mutation in *p53* had only a third of the survival rate of patients in clinical stage III with normal *p53* expression. Another good example is the 5-year survival of only 54% for stage II patients with allelic loss of chromosome 18q (mutation/loss of deletion in colorectal carcinoma (DCC)) in comparison with patients without loss of heterozygosity who had 93% survival [15]. In addition, the CD 95 receptor and ligand system seems to be of major importance, as well as the inhibition of local immunity probably induced by abundant expression of Fas ligand [30, 31], leading to cell killing.

From these data there is clear evidence that one main task of the present and future studies is to define the value and relevance of these factors for the selection of patients who will gain the most benefit from adjuvant chemotherapy. However, the mechanism of resistance to the chosen chemotherapy is of major importance, as has been recently shown for the expression of thymidylate synthase in primary tumour tissue [37] in a cohort of patients from an adjuvant chemotherapy study. Therefore, the proper selection of patients based on clinicopathological as well as molecular factors, particularly in stage II, is only one solution to improve the benefit and results of adjuvant treatment in colon cancer. The other solution is to apply combination chemotherapy regimes with drugs exhibiting different modes of action, e.g. a combination of 5-FU plus either oxaliplatin or irinotecan [38–40].

In conclusion, there are standard treatments for adjuvant chemotherapy in resected high risk colon cancer whose application is mandatory. However, we have the means in our hands for a better selection of patients for adjuvant treatment as well as for an improvement of the treatment protocols. This is an important and major task which requires large clinical trials, for example the European PETACC trial, with proper identification of patients according to potential prognostic factors and additional retrospective analysis of further molecular factors with potential predictive value. Such an important task needs a large international Intergroup collaborative effort, since this is the only way to achieve conclusions within a meaningful time-frame.

Table 4. *Five-year survival in stage II and III colorectal cancer in relation to different prognostic factors*

Five-year survival	Stage II (%)	Stage III (%)	Reference
CEA (ng/ml)			[11]
< 5	95%	n.s.	
5–10	80	n.s.	
10–20	60	n.s.	
> 20	45	n.s.	
p53 mutation			[28]
No *p53* mutation	71	63	
p53 mutation	55	26	
LOH in *DCC* (18q)			[15]
No loss	93	52	
Allelic loss	54	38	
NK cell infiltration			[31]
High	100	80	
Low	67	13	

ns, not stated; CEA, carcinoembryonic antigen; LOH, loss of heterozygosity; NK cell, natural killer cell.

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