Adjuvant treatment for colorectal cancer

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Abstract

Colorectal cancer is a leading cause of cancer in Western countries. Surgery remains the only way to cure it. Recent trials led to the general acceptance of adjuvant chemotherapy in Dukes C cancer by identifying bolus 5FU and leucovin during 6 months (5 days monthly) as the current standard. The role of adjuvant chemotherapy remains questionable in Dukes B2 (stage II) colon cancer, in rectal cancer and after curative resection of liver metastases.

The development of total mesorectum excision (TME) technique has dramatically resulted in improving local recurrence control and will be the standard in rectal cancer surgery ; preoperative irradiation is widely used in Europe for stage II and III rectal cancer but its definite place and its optimal regimen await further assessment as well as the role of adjuvant chemotherapy in rectal cancer.

New chemotherapeutic combinations based on new effective agents in colorectal cancer such as CPT-11 and oxaliplatine have been currently used for downstaging liver metastases initially unresectable. This new approach, combined with the development of local ablative therapies such as cryotherapy and radiofrequency allows curative strategies in a significant number of patients primarily unfit for surgical resection of liver mets.

The present paper aims to review the different aspect of (neo)adjuvant therapies in the multimodal curative management of colorectal cancers. (Acta gastroenterol. belg., **2001**, 64, **263-267**).

Colorectal cancer is the second leading cause of cancer deaths in Western countries (1). Surgery is the only way to cure and recurrence risk and survival are directly related to the pathological tumoral stage, reported in the Dukes' classification recently modified by Astler-Coller ; 5-year survival varies from 80-90% (Dukes A to B1) to 30-50% (Dukes C2) while in metastatic stage 5-year survival is less than 5% (2) (Table 1).

Recent trials led to the general acceptance of adjuvant chemotherapy in Dukes C colon cancer while the indication of adjuvant treatment in elderly patients, Dukes B2 patients and patients with resectable metastases remains questionable. Also in rectal cancer, treatment modalities remain discussed and are different in Europe and USA.

The present paper is reviewing the recent results and strategies reported in this field, including the use of new drugs.

Adjuvant chemotherapy for Dukes C colon cancer

Large cooperative group trials in Europe and US have shown a significant benefit for adjuvant chemotherapy as compared to surgery alone (3-5). Chemotherapy-based regimens mainly consisted in 5FU/levamisole during 12 months and 5FU/leucovorin during 6 months.

More recently, results from two large scale US studies (NSABP-04 and INT-089) have reported that 5FU/leucovorin is equivalent to 5FU/levamisole or 5FU/leucovorin/levamisole combined (6,7). The NSABP trial revealed a disease-free survival advantage for 5FU/leucovorin over 5FU/levamisole (6). Furthermore, a 12-months treatment was not superior to 6 months therapy and low-dose leucovorin (monthly or Mayo regimen) seems to be equivalent to high-dose (weekly or Roswell regimen) in modulating 5FU (8). Table 2 summarizes the major trials on adjuvant chemotherapy.

In conclusion, 5FU/leucovorin for 6 months is the most widely accepted standard regime in adjuvant therapy ; the risk of recurrence is globally decreased by 30% and the overall survival increased by 10-15%.

Dukes B2 colon cancer

Indication of adjuvant chemotherapy in stage II or Dukes B2 (T_3T_4-N_0) remains controversial due to the lack of large pure studies with only stage II cancers. In the majority of large trials, stage II colon cancer only represents a small number by comparison with stage III.

Two recent studies, one by pooling the number of B2 patients from 4 NSABP studies suggested a clear benefit for those patients, similar to that reported for Dukes C stage (9). Another pooled study, however, did not draw the same conclusions (10).

Specific immunotherapy might be also beneficial for B2 stage and one study reported a prolonged disease-free-survival for this stage in 170 patients (11). Based on the good results reported in Dukes C patients (12), a specific study with the monoclonal antibody 17-1A (Panorex) in Dukes B2 was recently initiated.

Another attractive way to identify B2 patients at high risk of recurrence is the detection of lymph node, bone medullar or circulating micrometastases using RT-PCR techniques for carcinoembryogenic antigen (CEA) mRNA or cytokeratine antigens (13). Identification and

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Presented at "the President's symposium" (june 2000).

Table 1. — **Pathological staging classification and survival data for colon cancer following surgery alone**

TMM stage	*Dukes' stage*	*Tumor*	*N° of nodes*	*Metastases*	*5-y survival (%)*
0-I	A/B1	Tis, T1, T2	0 (N0)	0	> 80
II	B2	T3	0	0	> 80
	B2	T4	0	0	75
III	C1	T2	1-4 (N1)	0	75
		> 4 (N2)	0	0	50
	C2	T3, T4	1-4	0	50
			> 4	0	30
IV		Any	Any	1	< 5

Table 2. — **Adjuvant treatment of colon cancer : main 5-FU/LV randomized trials**

Trial/Ref.	*Treatment/Control (mg/m²) duration*	*Patients (n)*	*Median Follow-up (months)*	*DFS% 5FU(LV)/Control*	*OS% 5FU(LV)/Control*
IMPACT (5)	5FU-LV vs 0 6 months (m)	1487	37	71 vs 62 p = 0.0001	83 78 p = 0.029
NSAB-C04 (6)	5FU-LV vs 5FU-Lev vs 5FU-Lev-LV 6 m	2151	63	64 vs 60 vs 64 p < 0.05	74 vs 69 vs 72 p < 0.05
MAYO (3)	5FU-LV vs 0 6 m	273	42	77 vs 64 p = 0.004	75 vs 71 p = 0.13
MAYO (8)	5FU-Lev 12 m vs 5FU-Lev 6 m vs 5FU-LV-Lev 12 m vs 5FU-LV-Lev 6 m	891	61	65 vs 60 vs 58 vs 63 p = NS	64 vs 59 vs 61 vs 69 P < 0.05
INT 0089 (7)	5FU-Lev 12 m 5FU-LDLV 7-8 m 5FU-HDLv 7-8 m 5FU-LDLV-Lev 7-8 m	3759	60	56 60 59 60 P < 0.05	63 66 65 67 P < 0.05

characterization of other biological markers as prognostic factors predicting recurrence or chemotherapy sensitivity is also reported : the thymidilate synthase (TS) as well as dihydropyrimidine dehydrogenase (DPD) expression levels inversely correlate with sensitivity and response to 5FU and could be of prognostic value in the adjuvant setting (14-16) ; detection of microsatellite instability (MSI) was just reported to be correlated to the prognosis of colon cancer and the benefit of adjuvant chemotherapy (17).

All these methods will help the clinicians to identify in the near future patients at high risk of recurrence who will benefit from adjuvant chemotherapy.

Regional adjuvant chemotherapy

Portal vein or intraperitoneal infusion of cytotoxic drugs (mainly mitomycine C and 5FU) have been developed over these last years. Results of different randomised studies were generally negative including the last ones from the EORTC and the Swiss group SAKK (18,19). Only a metaanalysis pooling the updated results of nine studies (4437 patients) shows a very small but significant survival benefit with regional therapy (absolute increase risk of 3.6% at 5-year survival) (20).

The question of a potential benefit by combining perioperative regional therapy and systemic chemotherapy was addressed in a recent large intergroup trial (EORTC + FFCD) : the results are awaited but in the era of new emerging drugs it does not appear likely that such approaches will open new perspectives.

Adjuvant chemotherapy in elderly patients

Many patients suffering from colorectal cancer are more than 70 years old and the question of administering adjuvant chemotherapy remains difficult to answer for clinicians in charge of such patients ; benefit appears uncertain and toxicity is feared.

A recent metaanalysis, analyzing patients more than 70 year old from 7 large trials (n = 3351 patients) showed that the benefit of survival is not reduced for older patients and that toxicity is not increased (except in one trial for neutropenia) in patients with good

performance status and normal liver and renal functions (21). Similar data were observed in both adjuvant and advanced settings in patients treated with the Mayo regimen (22).

Ongoing trials with new agents

The emergence of new drugs such as CPT-11 (Campto®), oxaliplatine (Eloxatine®), raltitrexed (Tomudex®) and oral 5FU prodrugs has lead to design new adjuvant trials.

The use of infusional 5FU mainly in Europe, reporting a higher response rate than bolus 5FU (23) and the development of combination with CPT-11 or oxaliplatine with 5FU and leucovorin in advanced disease, resulting in response rate around 50% and prolonged survival (for CPT-11/5FU/LV), has led to assess these regiments in the adjuvant setting (24,25).

Moreover, the activity of 5FU oral prodrugs such as UFT (tegafur + uracil, Orzel®) or capecitabine (Xeloda®) has been reported to be equivalent to 5FU/LV bolus regimen but less toxic (26). Assessment of these more convenient chemotherapy modalities is also currently ongoing in adjuvant trials. Table 3 reports a list of new adjuvant trials in Europe and in USA.

Table 3. — **New adjuvant trials in colon cancer**

- Panorex trial (mAb 17-1A) (GlaxoWellcome)
- UFT (Orzel®) vs Mayo regimen (NSABP-06)
- 5 FU/LV infusional/bolus ± oxaliplatin : Mosaic (Sanofi)/ NSABP-07
- 5 FU/LV infusional vs bolus : PETACC-2 trial
- 5 FU/LV infusional ± CPT-11 : PETACC-3 trial/Aventis
- 5 FU/LV/CPT-11 vs 0 in Dukes B2 stage
- Capecitabine vs Mayo (Roche)
- Capecitabine vs Mayo ± CPT-11 : Quasar-2 trial (UK)

Adjuvant treatment of rectal cancer

Adjuvant treatment of rectal cancer should be ideally considered under a different view since the paramount factors of good prognosis are clearly surgery and ... the surgeon (27). For many years, surgical excision alone had been however somewhat disappointing for local control of stage II (B2) and III (Dukes C) rectal cancers, as shown by local recurrences rate of 20-40% observed (28).

Better knowledge of microscopic lymphatic spread within the mesorectum has led to the development of total mesorectum excision (TME) for mid and low rectal tumours, notably by Heald and coll (29). After TME, local recurrence rates have decreased to < 10% and despite the absence of prospective controlled studies, this technique is now considered as the gold standard for resection of carcinoma affecting the middle and lower third of the rectum.

Classical adjuvant therapy for rectal cancer usually consists in administering preoperative radiotherapy, as widely admitted in Europe.

European investigations, mainly from Scandinavia, have advocated preoperative intensive short courses of irradiation (25 Gy in one week) immediately followed by surgery and reported beneficial results on local recurrence rate and survival even in early stage of cancer (30). However, there are many concerns against this regimen as raised by radiotherapists advocating conventional (50 Gy) six-week preoperative irradiation : all stages have been treated and therefore early stages could be overtreated ; there was no enhancement in the percentage of patients who can undergo sphincter preservation, as opposed to conventional irradiation and increased toxicity and late functional complications can be observed. Therefore in Europe, preoperative radiotherapy using the 45-50 Gy five to six week irradiation regimen is considered as the standard while it is premature to advocate combination of chemotherapy and radiotherapy and to recommend a short intensive irradiation regimen (31). Moreover, the results from a randomized Dutch trial comparing TME plus or minus preoperative irradiation (2000 patients) will be of major interest since they will show if radiotherapy continues to add some benefit to the newly defined standard "TME" surgery.

In US, the recommended strategy is postoperative irradiation combined with chemotherapy ; this emerged from large randomized studies also showing a benefit in terms of local recurrence rate and survival for combined modality treatment (32). In this setting, continuous infusional 5FU was shown to be superior to 5FU bolus in terms of survival advantage and this combination is currently the standard in US (33).

Future trials will aim to assess the place and the sequence of combined treatment (preoperative chemoradiotherapy vs postoperative chemoradiotherapy, adjuvant chemotherapy to preoperative radiotherapy + TME, new radiosensitizing agent active in colorectal cancer such as CPT-11, raltitrexed, oxaliplatine, oral capecitabine...).

So far, the place of adjuvant chemotherapy in rectal cancer remains questionable since the large adjuvant studies have only enrolled a limited percentage of rectal cancers as compared to colon cancers. Also, the benefit of a locoregional chemotherapy was never proved. Nevertheless, by analogy to colon cancer, it is generally admitted that adjuvant chemotherapy (six months Mayo regimen) can be proposed in stage III rectal cancer.

(Neo)adjuvant chemotherapy for cure of liver metastases

Liver metastases are found in around 50% of patients with a colorectal cancer and the liver is the unique site of initial tumor recurrence in up to 30% of patients with metastatic diseases ; the frequency of synchronous colorectal liver metastases is 15-30% which is the same to the frequency of metachronous metastases usually developed within a period of 3 years (34,35). For colorectal liver metastases, surgery is currently the only

potential curative treatment but resection can be performed in only 10% of all patients. Perioperative morbidity and mortality are very low in specialized center (1-2%), and curative resection results in 5-year survival around 30% (36,37). Factors influencing the prognosis are TNM stage of primary tumor (lymph node involvement), resection margin < 1 cm at hepatectomy, tumor size, number of metastases (< 4), synchronous disease, high preoperative levels of CEA, previous adjuvant chemotherapy (38-41).

In the setting of resectable liver metastases, there is no clear demonstration that adding chemotherapy is of valuable benefit. The role of adjuvant systemic and/or intrahepatic chemotherapy have been addressed after liver mets resection in only small studies and results are discrepancing.

There is only one study showing an advantage for intraarterial chemotherapy on systemic therapy in terms of progression free survival and 2-year survival for patients having a median number of 3 liver metastases but the series was relatively limited and both patients and expertise centers highly selected (41).

The majority of patients with colorectal liver metastases present with non resectable tumors at the time of diagnosis ; for these, the treatment only consists in chemotherapy. New combinations based on new emerging drugs such as CPT-11 and oxaliplatine and infusional 5FU and folinic acid have shown interesting activity (response rate $\approx$ 50%) in first line therapy but only a slight increase in overall survival (from 12 to 17 months) (24,25). The use of such active combination, as especially reported by using oxaliplatin and 5FU/leucovorin chromomodulated can downstage tumor growth and makes it possible to perform curative resection in patients initially ineligible for curative surgery. Results reported by the Paul Brousse Center are extremely promising showing that resection became possible in 53 of 330 patients (16%) and that 5-year survival in these patients treated by neoadjuvant chemotherapy was the same (around 40%) to that of patients initially resectable (42). Another report from the same team confirmed this strategy by observing a complete resection rate of 38% (58/151 patients) after neoadjuvant chemotherapy (43).

This multimodal approach is also supported by the development of new other "adjuvant" treatment combined to surgery. Cryotherapy and radiofrequency can be used to locally destroy tumor that cannot be resected and can be considered as an adjunct to resection with curative intent.

Feasibility studies have been published and results appear promising in terms of local control of tumor (44,45). Further studies are in development to assess the place of such procedures as compared to chemotherapy alone. Anyway, these approaches combined with resection and performed after chemotherapy would probably increase the number of indications of curative strategies in patients primarily unfit for a complete surgical resection.

Conclusions

Significant progresses have been achieved in the multimodal management of colorectal cancers resulting in increased progression free survival and overall survival. These improvements consist in optimization of both surgery and (neo)adjuvant chemotherapy based on new active drugs.

Other fields of research will aim to identify new biological and molecular markers that correlate with tumor prognosis and that predict response to chemotherapy.

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