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Current Controversies in Cancer

Should Patients with Advanced Colorectal Cancer be Treated with Chemotherapy?

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INTRODUCTION

MANY PATIENTS with advanced or metastatic colorectal cancer die without having received chemotherapy. The main reason for this is scepticism on the part of their physician regarding the possible benefits of such treatment. This scepticism is justified. In the literature, response rates after treatment with 5-fluorouracil (5-FU) vary between 8% and 85%, a phenomenon that has not encouraged the confidence of practitioners in the true value of chemotherapy [1]. Moreover, in 38 phase II studies carried out before 1984 in the U.S.A., not a single new drug was able to achieve a response rate exceeding 20%, making colorectal cancer a more resistant disease than even non-small-cell lung cancer and malignant melanoma [2].

Things did not improve greatly after new approaches to 5-FU therapy, such as continuous infusions and biochemical modulation, had been subjected to rigorous phase III testing. The SWOG screening study did not show major differences between seven treatment arms nor did two large meta-analyses of modulation with leucovorin or methotrexate reveal major survival differences, if any at all [3–5].

Negative results thus prevail in the literature on the treatment of patients with metastatic colorectal cancer. The question to be addressed in this controversy paper is: may our scepticism have clouded our view on the true beneficial effect of chemotherapy compared to approaches such as best supportive care. Results from four studies suggest that this may indeed be the case.

PROLONGATION OF SURVIVAL BY CHEMOTHERAPY

In Table 1 response and survival data are summarised from studies comparing liver-directed chemotherapy with a control group [6, 7]. In the Swedish study, controls received best supportive care. In the British study, controls could, in addition, receive systemic chemotherapy, but only 20% of patients received such treatment at any time during their remaining life. In these studies, the treated patients survived, on average, 5.5–7.5 months longer than those not treated.

In two other studies, systemic 5-FU-based cytotoxic treatment was compared with controls [8, 9] (Table 2). In the study by the Nordic group, only asymptomatic patients were included, who were randomised to receive immediate chemotherapy or to wait until symptoms justified such treatment; this was actually given in 57% of these "expectancy" patients. Treatment added on average 5–6 months to the duration of survival. Given the design of the Nordic study, the 5 months difference should be considered a minimum. Taken together, these data strongly suggest that 5-FU based chemotherapy adds at least 6 months to the remaining life of patients with metastatic colorectal cancer. In all studies, this means almost a doubling of survival time.

QUALITY OF LIFE AND TOXICITY

If chemotherapy prolongs survival, what is the value of this prolongation for the patient? In three of the four mentioned studies, this issue was addressed. In the studies by Schreithauer and associates [9] and Allen-Mersh and associates [6], formal quality of life analyses were performed. In both studies the prolongation of survival was not paid for by a deterioration of its quality.

In the Nordic study of asymptomatic patients and the British study, in which 80% of the patients were asymptomatic, the effect of early and immediate treatment on the prolongation of the physical symptom-free survival could be studied [6, 8]. Results are summarised in Table 3 and clearly show that the asymptomatic state was prolonged by 3–9 months to approximately 10–11 months. The difference in symptom-free survival between the control groups is probably due to patient selection. The Nordic study included over 50% of patients with extrahepatic disease, which may lead more quickly to symptoms than is the case with disease that is limited to intrahepatic metastases.

Table 1. Intrahepatic chemotherapy versus no treatment in metastatic colorectal cancer

Study	Number of patients	Response rate	Median survival (months)	*P* value
Allen-Mersh and associates [6]				
No treatment	51	–	7.5	
versus				0.03
HAI floxuridine	49	40%	13	
Hafström and associates [7]				
No treatment	26	–	8.5	
versus				0.004
HA occlusion + PVI 5-FU	28	25%	16	

HAI, hepatic artery infusion; PVI, portal vein infusion.

Table 2. Systemic chemotherapy versus no or delayed treatment in metastatic colorectal cancer

Study	Number of patients	Response rate	Median survival (months)	*P*-value
Nordic Group [8]				
Expectancy	90	–	9	
versus				0.02
MFL	92	28%	14	
Schreithauer and associates [9]				
No treatment	12	–	5	
versus				0.006
FL/CDDP	24	33%	11	

MFL, methotrexate, 5-FU, leucovorin; FL/CDDP, 5-FU, leucovorin, cisplatin.

Finally, several studies have addressed the issue of the subjective response. In another study from the Nordic Group [10], 198 symptomatic patients were treated with 5-FU based chemotherapy. Although the response rate was only 19%, 40% of these patients had a total disappearance or considerable improvement of tumour-related symptoms without severe adverse effects (Table 4). This subjective response lasted for almost 9 months.

If we take these data together, chemotherapy appears to delay the occurrence or aggravation of symptoms in 40–50% of patients by 9–11 months. Two factors probably contribute significantly to this positive effect. The first is early treatment; most data have been obtained in asymptomatic patients [6, 8] and symptomatic improvement occurred more frequently in patients with a good performance status (Table 4). The second factor is the low toxicity of the chemotherapeutic regimens. In the Nordic study, using the combination of 5-FU, methotrexate and leucovorin, grade 3–4 leucopenia, stomatitis and diarrhoea each occurred in less than 10% of patients [8]. Similar results were obtained in the EORTC study of high-dose 48-h infusions of 5-FU with or without methotrexate. The highest level of toxicity was seen for stomatitis, which was severe in 10% of patients receiving 5-FU plus methotrexate [11]. These toxicity data compare favourably with those seen with the two widely applied 5-FU plus leucovorin combinations [12].

Table 3. Chemotherapy in metastatic colorectal cancer: prolongation of physical symptom-free survival

	Number of patients	Median symptom-free survival (months)	*P* value
Nordic Group [8]			
Expectancy	90	2	
versus			<0.001
MFL	92	11	
Allen-Mersh and associates [6]			
No treatment	51	7	
versus			<0.05
HAI floxuridine	49	10	

THE SIGNIFICANCE OF STABLE DISEASE

Why is it that, with response rates below 30% and in many studies below 20%, chemotherapy appears to almost double the survival time of the entire population? One

Table 4. Metastatic colorectal cancer: proportion of patients with total disappearance or improvement of tumour-related symptoms and no severe adverse effects [10]

All patients	40%
Treatment	
MFL	45%
FL	37%
KPS	
90	57%
50–60	34%
Response	
Partial response (19%)	97%
Stable disease (24%)	64%

MFL, methotrexate, 5-FU, leucovorin; FL, 5-FU, leucovorin; KPS, Karnofsky performance status.

Table 5. Standard chemotherapy for metastatic colorectal cancer

Infusional 5-FU
5-FU modulated with LV or MTX
Tomudex

LV, leucovorin; MTX, methotrexate.

reason may be that in colorectal cancer stabilisation of disease is a clinically relevant effect of chemotherapy. Indeed, in the study of Schreithauer and associates [9], the difference between the two arms was considerable if disease stabilisation was taken into account. Early progression was observed in 75% of the control as opposed to 25% of the treated patients. The clinical significance of this finding can be estimated from data from the study of the Nordic Group in symptomatic patients [10]. Of the patients with stabilisation of disease or partial response (43% of the population), 79% showed symptomatic improvement (Table 4). In a small, unpublished study of patients treated with chemotherapy for synchronous liver metastases, Wagener and associates [11] found that the survival time of responding and stable patients was not different with a median of slightly over 24 months. Stabilisation of disease is a meaningful result in the chemotherapy of colorectal cancer, which is associated with improvement of symptoms and survival.

WHAT IS STANDARD CHEMOTHERAPY (TABLE 5)

Many 5-FU based chemotherapy regimens have been administered to patients and, as shown by the SWOG and other studies mentioned before, there is no clearly superior regimen as far as survival is concerned. Two factors should play a role in making the right choice: dose intensity and toxicity. In particular, in the adjuvant setting, the dose of 5-FU given over a specific time appears to be a determinant of therapeutic effect [13]. For response rates, dose-intense infusional 5-FU is superior to bolus 5-FU [14]. Moreover, infusion 5-FU has a very favourable toxicity profile, both if given over weeks or as 24- or 48-h infusions every week [11]. In the meta-analyses, 5-FU treatment escalated to maximal doses showed similar response rates and survival as lower doses of 5-FU modulated with leucovorin or methotrexate [4, 5]. These treatments should, therefore, be considered equivalent to infusional 5-FU and are acceptable standard chemotherapy, although their toxicity may be higher. Data on modulated dose-intense infusional 5-FU are promising [15]. Finally the new thymidylate synthase inhibitor, Tomudex, appears to be equally effective and less toxic than bolus 5-FU modulated by low-dose leucovorin [16]. Its easy route of administration makes this drug an attractive alternative for standard treatment.

CONCLUSION

Chemotherapy for advanced or metastatic colorectal cancer prolongs survival by 6 months, delays the occurrence or progression of symptoms by 6 months and improves symptoms without severe toxicity in 40% of patients. It is important to start early and to continue treatment in case of stabilisation of disease. It should be offered to any patient with the disease who can tolerate the relatively mild toxicity of treatments such as infusional 5-FU, modulated 5-FU or Tomudex. The results of this treatment may be further improved by studying combinations of (infusional) 5-FU with Tomudex, topoisomerase-1 inhibitors, new biochemical modulators and experimental platinum compounds.

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