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Combined Adjuvant Therapy of Radically Operated Colorectal Cancer Patients

(Chemotherapy, Radiotherapy, and MER-BCG)

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Summary. *Seventy-three patients with Dukes' B_2 and C colorectal cancer were randomized to adjuvant therapy after radical surgery. One group was treated with chemotherapy either alone or in combination with radiotherapy (RC). The second group was treated by chemotherapy (with or without radiotherapy) plus MER/BCG (RCM). In patients with Dukes' C disease, the survival at 54 months and the disease-free interval up to 24 months were significantly better in the RCM than in the RC subgroup. There were no significant differences in the survival and disease-free interval between RC- and RCM-treated patients with Dukes' B_2 disease. Entry of additional patients and further follow-up are needed before we can decide whether the combination of RCM increases the cure rate in Dukes' C cancer or merely delays recurrence and prolongs survival.*

Introduction

The cure rate in large-bowel cancer has not been significantly altered over the past two decades [22]. The unrecognized minimal residual disease after surgery is responsible for recurrence and death. Adjuvant therapy has been shown to be an effective treatment for minimal disease in different malignant tumors [10]. In a nonrandomized study of colorectal cancer we found that adjuvant radio- and chemotherapy decreases the recurrence rate and increases survival [20].

Immunotherapy with BCG has been reported to prolong survival and increase disease-free interval in various neoplasms [13, 16]. MER, the methanol extraction residue of BCG, is a potent immunostimulant and has certain advantages over BCG [30, 31]. It has been used in the treatment of patients with advanced cancer [18].

In January 1975, an adjuvant trial comparing radiochemotherapy (RC) against radiochemotherapy plus MER (RCM) in patients with locally advanced and radically operated colorectal cancer was started at our center. A preliminary report demonstrating an improvement in the 2-year survival and disease-free interval for the RCM-treated patients has been published [21]. In the present paper we report the long-term follow-up of 73 patients analyzed in January 1981.

Materials and Methods

Patients. Seventy-three patients who had undergone curative surgery for colorectal cancer were admitted to this study. The following criteria were used for patient selection: (1) A biopsy-proven diagnosis of stage B_2 adenocarcinoma of the rectosigmoid or stage C colon and rectosigmoid cancer (according to the Astler and Coller modification of the Dukes' classification); (2) Age below 75 years; and (3) Performance status of 70% or more according to the Karnofsky scale. After giving informed consent, the patients were stratified according to stage, localization, age, and sex, and randomized to a group to be treated with RC or a second group whose members received RCM. Forty-four patients had Dukes' C colorectal cancer and 29, Dukes' B_2 rectosigmoid cancer. The major characteristics of these patients are summarized in Tables 1 and 2: The RCM and RC subgroups were similar, except that in stage B_2 the female/male ratio was higher in the RC-treated than in the RCM-treated patients.

Therapy

Chemotherapy. 5-Fluorouracil (5FU) 13.5 mg/kg was administered IV for 5 days, starting 3–6 weeks after surgery, and later every 5 weeks for 18 months.

Radiotherapy. The radiotherapy was started after the first course of 5FU: 4,000 rads in 4 weeks were administered to the pelvis or lower

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Table 1. Characteristics and treatment results of patients with Dukes' C colorectal cancer

	Radiochemotherapy + MER	Radiochemotherapy
No. of patients	22	22
Age: range (mean)	26–69 (58.2)	46–73 (61.0)
Female/male ratio	12/10 (1.2)	12/10 (1.2)
Localization { Rectosigmoid	13 (59.1%)	14 (63.6%)
Localization { Other sites	9 (40.9%)	8 (36.4%)
Follow-up in months; range (mean)	6–72 (38.6)	6–72 (38.4)
Actuarial survival at 54 months	78%	26% ($P < 0.01$)
Disease-free interval at 54 months	53%	25% (NS[a]; at 24 months $P < 0.05$)
Patiets with recurrent disease (localization: colorectal)	8 (36.4%)	12 (54.5%)
Patients with recurrent diseae (localization rectosigmoid)	5 (38.5%)	8 (57.1%)

[a] Not significant

Table 2. Characteristics and treatment results of patients with Dukes' B_2 rectosigmoid cancer

	Radiochemotherapy + MER	Radiochemotherapy
No. of patients	13	16
Age: range (mean)	36–70 (59.6)	29–68 (57.1)
Female/male ratio	6/7 (0.86)	10/6 (1.7)
Follow-up in months: range (mean)	9–68 (39.2)	7–69 (32.4)
Actuarial survival at 48 months	55%	61% (NS)[a]
Disease-free interval	46%	31% (NS)[a]
Patients with recurrent disease	6 (46.2%)	6 (37.5%)

[a] Not significant

abdomen through two opposing fields by Co-60 or 10 MeV linear accelerator (only in patients with rectosigmoid cancer).

MER-BCG. Phipps strain was generously supplied by the Division of Cancer Treatment, National Cancer Institute, NIH, in ampules containing 1 mg/ml. MER was injected 2 weeks after the second course of chemotherapy in patients treated with radiotherapy, and after the first course in patients not receiving radiotherapy. Courses were repeated every 4–5 weeks between the 5FU courses. The standard dose of MER was 0.1 mg per injection site. MER was given ID on the back or arms of the patients at ten injection sites. Prior to the MER injection a skin test to four different dilutions of MER was done (1 : 1, 1 : 10, 1 : 100, and 1 : 1000 of the original solution). The dose of MER was determined according to the skin reactivity. The dose that led to approximately a 1-cm inflammatory lesion with central necrosis was chosen as the treatment dose. Highly reactive patients received a low dose and weakly reactive patients, a high dose. The number of treatments ranged between 3 and 20 (mean 10.2) for Dukes' C patients and between 3 and 21 (mean 10.9) for Dukes' B_2 patients.

The routine follow-up included physical examination every 2–3 months, liver function studies, occult blood in the feces and CEA determinations every 4 months, chest film every 6 months, and barium enema every 12 months.

Statistical Analysis. The patient survival data were analyzed according to the actuarial survival curves. The differences in survival between the combined MER-treated and control groups were tested by the Z-test, this evaluation being a compouter-assisted.

Results

Dukes' C

Figure 1 and Table 1 show the actuarial survival and disease-free interval in Dukes' C colorectal cancer patients measured from the time of operation. The survival at 54 months was 78% in the RCM subgroup and 26% in the RC subgroup. This difference was statistically significant ($P < 0.01$). The disease-free interval was significantly better in the RCM subgroup than in the RC subgroup up to 24 months ($P < 0.05$),

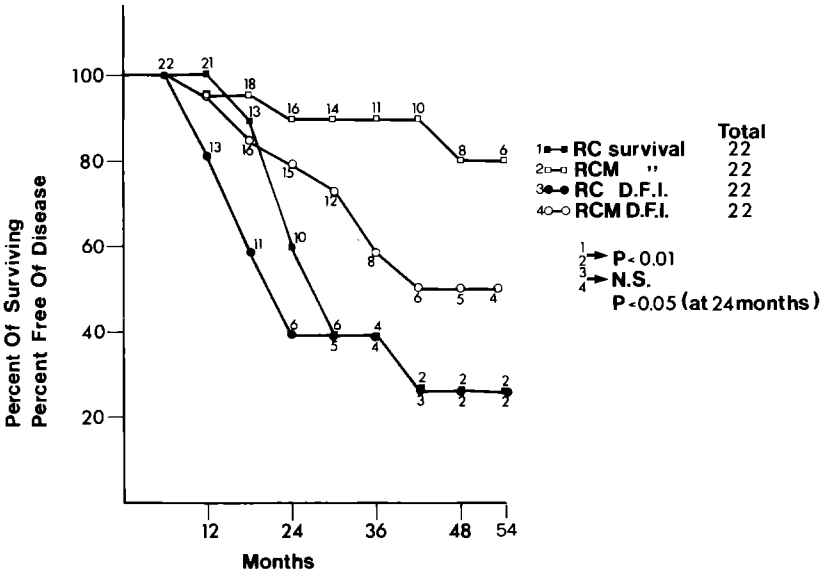

Fig. 1. Actuarial survival and disease-free interval (D.F.I.) of Dukes' C colorectal cancer patients

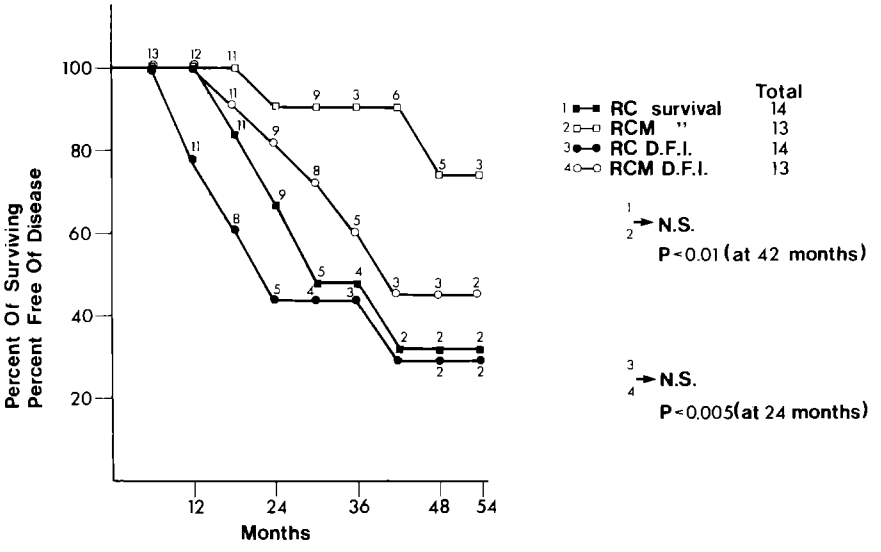

Fig. 2. Actuarial survival and disease-free interval (D.F.I.) of Dukes' C rectosigmoid cancer patients

although at 54 months this difference was no longer significant (53% for the RCM-treated and 25% for the RC-treated patients).

A separate analysis of the results was performed according to the tumor localization. The actuarial survival and disease-free interval in Dukes' C recto-sigmoid cancer patients are presented in Fig. 2. The survival at 42 months was significantly better in the RCM-treated patients than in those treated with RC ($P < 0.01$). At 54 months survival was also obviously better in RCM (75%) than in the RC group (32%), but this difference was no longer significant. The disease-free interval was significantly better in the RCM- than in the RC-treated patients at 24 months ($P < 0.05$). At 54 months the disease-free interval in the RCM-treated patients (46%) was better than in RC patients (29%), but the difference was not statistically significant.

In Dukes' C carcinoma of the proximal colon a better survival at 54 months was obtained in the nine patients treated with 5FU and MER (88%) than compared in the eight patients treated with 5FU alone (14%, $P < 0.01$). The disease-free interval was also better in the MER-treated patients (57%) than in those treated with 5FU alone (14%). This difference was not significant, however. It is possible that the lack of statistical significance is due to the small number of cases.

Table 3. Pattern of relapse in patients with rectosigmoid cancer

	No. of patients with pelvic recurrence	No. of patients with distant metastases	No. of patients with concomitant pelvic recurrence and distant metastases
RCM-treated Dukes' C patients	2	3	–
RC-treated Dukes' C patients	3	4	1
RCM-treated Dukes' B_2 patients	1	4	1
RC-treated Dukes' B_2 patients	2	4	–
	8 (32%)	15 (60%)	2 (8%)

Dukes' B_2

The survival and disease-free interval at 48 months were 55% and 46%, respectively, for the RCM patients and 61% and 31% in the RC patients. No significant differences between these subgroups were found.

Disease Recurrence

Table 1 shows that in patients with Dukes' C the disease recurred in eight (36.4%) of the RCM group, as against 12 (54.5%) of the RC group.

In patients with Dukes' B_2 disease a recurrence developed in six (46.2%) RCM-treated patients and in six (37.5%) RC-treated patients (Table 2).

The pattern of relapse in the 25 patients with rectosigmoid cancer (treated with pelvic irradiation) is shown in Table 3. Sixty percent (15 of 25) of the patients who relapsed presented with distant metastases, 32% (8 of 25) had pelvic recurrence alone, and 8% (2 of 25) had concomitant pelvic recurrence and distant metastases.

Discussion

Surgery is the preferred and best treatment of localized colonic cancer. However, when the tumor has spread to the serosa and/or lymph nodes the recurrence rate is 28%–50% and the 3-year survival is 20%–50% [2, 4, 5, 23, 25, 26, 28]. It is therefore justifiable to try adjuvant therapy in this group of patients.

Each of the three regimens we used has been studied extensively. However, to the best of our knowledge the triple combination has not been tried in an adjuvant system. Various reports have shown that preoperative and postoperative radiotherapy improved survival of patients with rectal cancer [7, 14, 22, 24, 27, 32]. Conflicting reports have appeared in the literature concerning the value of 5FU as an adjuvant treatment [1, 6, 9, 11, 15].

There are two main reasons for using immunotherapy combined with radiochemotherapy: (1) To reverse the immuno-incompetence encountered after radiochemotherapy; and (2) to augment the capacity of the immunologic system to destroy residual tumor cells. There have been only three reported studies on the use of adjuvant immunotherapy in colorectal cancer [12, 13, 21]. Mavligit et al. [13] reported that adjuvant BCG or BCG and 5FU increased the disease-free interval and prolonged survival in Dukes' C colorectal cancer patients compared with historical controls. In another randomized study, however, the disease-free interval and survival in patients with colon cancer treated by adjuvant chemotherapy or chemotherapy combined with MER were similar [12]. The immunostimulant we have been using is MER. In mice bearing malignant tumors, MER combined with chemotherapy and radiotherapy was more effective in prolonging survival and reducing tumor volume than radiotherapy and chemotherapy [30]. In humans with advanced neoplasia MER has been shown to be a stimulant to the immune system [18].

In a randomized trial in patients with advanced lung cancer there was no statistically significant difference in survival between those treated with radiochemotherapy plus MER and those treated with radiochemotherapy only [19], but it was shown that MER stimulated the immune response. MER was well tolerated and no serious side-effects were

apparent. As immunotherapy is effective only on a minimal tumor load, our conclusion was that it is justifiable to give adjuvant immunotherapy combined with radio- and chemotherapy for recurrence in a high-risk group of patients.

The preliminary results of the current study as analyzed at 24 months showed that the addition of MER to the conventional treatment may have a therapeutic advantage [21]. The results of the longer follow-up presented in this study have confirmed the value of MER in adjuvant therapy of patients with Dukes' C colorectal cancer. On the other hand, no apparent therapeutic effect of MER was found in patients with Dukes' B_2 rectosigmoid cancer. The therapeutic advantage of MER therapy in Dukes' C disease was evident both in rectosigmoid cancer patients and in those with proximal colon cancer. Therefore, the lack of effectiveness of MER in rectosigmoid cancer Dukes' B_2 seems to be related to the stage of the disease. Mavligit et al. [13] found that adjuvant therapy with BCG was more effective in Dukes' C patients with six or more positive nodes than among patients with five or fewer positive nodes. They put forward the hypothesis that in human cancer there might be a minimal critical level of tumor burden below which BCG becomes ineffective, probably because of inadequate amounts of tumor antigen. Such a hypothesis provides a possible explanation for the different therapeutic effect of MER in Dukes' stage B_2 and in Dukes' stage C found in this study.

Local recurrence is more frequent than distant metastases in rectosigmoid cancer treated by surgery alone [2, 8]. Pelvic irradiation, however, reduces the local recurrence rate [22, 32]. In the present series of patients with rectosigmoid cancer, distant recurrence of the disease was obviously more frequent than pelvic recurrence. Such a pattern of relapse was evident in all subgroups with rectosigmoid cancer (i.e., RC, RCM, Dukes' B_2 and Dukes' C), and seems therefore to be a consequence of pelvic irradiation. The better survival and longer disease-free interval in the RCM group than in the RC group are most probably due to the MER therapy.

At the ASCO meeting in 1979, it was reported [12] by the Gastrointestinal Tumor Study Group that the disease-free interval and survival in patients with colon cancer treated with adjuvant chemotherapy or chemotherapy combined with MER were similar. The three main differences between the negative results of that study and the positive results of this present study are:

1) Cytotoxic therapy: The GI Tumor Study Group administered 5FU and methyl-CCNU; we gave 5FU and radiotherapy;

2) MER: The patients treated by the GI Tumor Study Group received a standard dose, and a dose modification was necessary due to toxicity in 85% of the patients. The patients in our study were given dosages of MER that were adjusted for their skin reaction to MER and there was very little toxicity;

3) Time of MER administration: In the GI Tumor Study Group's trial MER was given on the same day as the chemotherapy. Our patients were given MER 2 weeks after chemotherapy.

The importance of the time interval between chemotherapy and immunotherapy has been reported. In murine fibrosarcoma the best results were obtained when *C. parvum* was administered 12 days after chemotherapy. When the time interval was longer than 16 days no further effect was seen. When immunotherapy and chemotherapy were administered on the same day the combination was toxic [3].

In murine leukemia treated with BCNU combined with *C. granulosum* [17] and in murine fibrosarcoma and mammary carcinoma treated with cytotonhosphan and *C. parvum* [29] the best results were obtained when the time interval between chemotherapy and immunotherapy was between 9 and 12 days.

Any of the three differences between the protocols might explain the difference in the results. It is too early to assess whether our treatment merely delays recurrence and increases survival in Dukes' C colorectal cancer or whether it increases the cure rate. Entry of further patients in the study and longer follow-up are required before this question can be answered.

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