Results of a Randomized Trial with or without 5-FU-based Preoperative Chemotherapy followed by Postoperative Chemotherapy in Resected Colon and Rectal Carcinoma

The Colorectal Cancer Chemotherapy Study Group of Japan – The 2nd Trial*

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Background: Our previous study confirmed the efficacy of postoperative treatment with mitomycin C (MMC) and oral 5-fluorouracil (5-FU) for colorectal cancer. The 2nd trial was designed to evaluate the effectiveness of additional preoperative chemotherapy to postoperative treatment with MMC and oral 5-FU for curatively resected colorectal cancer patients.

Patients and Methods: 1355 patients (colon 755; rectum 600) were enrolled in this study. The pre- and postoperative chemotherapy (PPC) group was treated preoperatively with 5-FU (320 mg/m²/day) by continuous intravenous infusion for 5 days beginning on day 6 before surgery and postoperatively with MMC (6 mg/m²) on days 7 and 14 and in months 2, 4 and 6, by bolus injection and oral 5-FU (200 mg/day) for 6 months. The postoperative chemotherapy (PC) group received postoperative chemotherapy only.

Results: In an intent-to-treat analysis, the 5-year survival rate in the PPC group and the PC group was 77.3% and 75.7% for colon cancer and 67.2% and 69.2% for rectal cancer, respectively. In a per-protocol analysis, the 5-year DFS rate in the PPC group and the PC group was 76.0% and 80.7% for colon cancer and 60.5% and 63.0% for rectal cancer, respectively, indicating no significant differences between the two groups. Adverse reactions were generally mild, confirming the safety of this preoperative chemotherapeutic regimen.

Conclusion: In the PC group, the 5-year survival rate was nearly identical with that seen in our earlier research using the same regimen, reaffirming the clinical effectiveness of postoperative MMC by protracted intravenous infusion and oral 5-FU. However, our findings did not support additional preoperative chemotherapy for curative resection in patients with colorectal cancer.

Key words: 5-fluorouracil – preoperative chemotherapy – postoperative chemotherapy – colorectal cancer

INTRODUCTION

A number of randomized comparative studies have been performed in Japan to evaluate the effectiveness of postoperative chemotherapy in colorectal cancer (1). From 1984 through 1990, our group was among the first (2–4) to evaluate the effectiveness of postoperative chemotherapy. We selected patients who were scheduled to undergo a curative resection for colorectal cancer and then randomly allocated the patients into three groups: a group treated postoperatively with mitomycin C (MMC) by protracted intravenous infusion (6 mg/m² × 5) + oral 5-FU (200 mg/day for 6 months), a group for whom this treatment was augmented by administration of MMC through the portal vein or intra-arterially during surgery and a group treated with surgery alone. Localized administration of MMC showed no clinically significant benefits, but statistical analysis confirmed the effectiveness of postoperative MMC by protracted intravenous infusion + oral 5-FU.

Preoperative chemotherapy is sometimes performed with the hope of down-staging before undertaking surgical intervention into the vasculature or lymph ducts, to reduce the likelihood of tumor recurrence by decreasing the viability of the tumor cells or to act against hypothesized metastatic micro-lesions (5). In cancers that are highly sensitive to anticancer drugs, such as cancers of the head and neck and osteosarcoma, preoperative chemotherapy is widely used in a multidisciplinary approach to surgery for functional preservation (6,7).

Preoperative chemotherapy is thus being applied in a variety of treatment modalities to various forms of solid cancer. However, in colorectal cancer patients scheduled for curative resection, preoperative therapy is contraindicated if the toxicity associated with this treatment will lead to increased surgical time and/or a higher rate of postoperative complications. There is also a risk that the use of long-term preoperative therapy may result in a loss of the option for curative resection.

*For participating physicians and institutions, see Appendix.

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In this study, we implemented preoperative chemotherapy during the waiting period before surgery in order to evaluate the efficacy of preoperative chemotherapy. Since we had already evaluated the effectiveness of postoperative MMC and 5-FU in our earlier research, we used those findings to evaluate potential advantages of adding preoperative chemotherapy to postoperative MMC and 5-FU in comparison with postoperative chemotherapy only. We did this to provide a basis for comparison of the effectiveness of additional preoperative chemotherapy and also to confirm the reproducibility of our earlier clinical study.

Before beginning this research, we performed a pilot study to confirm the safety of a preoperative chemotherapeutic regimen. Based on the results of the phase I study published by Lokich et al. (8) using 5-FU by continuous intravenous infusion (CIV), we established a preoperative chemotherapy schedule of 5-FU (320 mg/m²) CIV for 3–7 days or 5-FU (320 mg/m²) IV for 5 days (unpublished data). We found that 5-FU CIV for 5 days had a slight histological response and still maintained effective antineoplastic drug levels in the tumor and blood, so we adopted this regimen for the preoperative chemotherapy used in this study.

PATIENTS AND METHODS

ELIGIBILITY

To be eligible for this study, a patient preoperatively had to meet the following criteria: a histologically proven colorectal cancer; a suitable candidate for surgery; no evidence of distant metastasis; tumor depth of at least SS (subserosal, tumor invasion through the muscularis propia into the subserosa) or T1 (tumor invasion into the muscularis propia without further penetration) or diagnostic imaging showing lymphatic metastasis; a curatively resectable tumor; age <70 years; no prior cancer; no double or multiple cancer present; laboratory test values generally within the range of WBC count ≥4000/μl, Hb ≥11.0 g/dl, PLT ≥100 000/μl, AST ≤40 U and ALT ≤40 U, BUN ≤25 mg/dl and negative urinary protein; performance status of 0–1; no serious complications such as heart disease, hepatopathy, nephropathy, myelosuppression, infection, varicella, gastric ulcers or bleeding; patient not pregnant or potentially pregnant; at least 5 days remaining before the scheduled date of surgery; and informed consent obtained from the patient or patient’s family.

Patients were considered ineligible after enrollment if the histological findings after surgery were non-cancerous; double or multiple cancer was discovered within 6 months after surgery; or the case review committee judged that for some other reason the patient was not suitable for analysis.

Data on the patients who met the above criteria were analyzed by intent-to-treat. They were further analyzed by per-protocol analysis unless the disease was found to be Duke’s stage A after surgery; macroscopic or histological findings indicated that the tumor was non-resectable; or the patient died within 1 month after surgery.

All surgical and histopathological findings were described in accordance with the General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus (4th Edition) (9).

STRATIFICATION AND RANDOMIZATION

Patients who met the criteria for eligibility were enrolled with the central registry. The patient pool was stratified according to cancer site (colon or rectum) and preoperative carcinoembryonic antigen (CEA) level. The enrolled patients were then randomly allocated to receive either pre- and postoperative chemotherapy (PPC) or postoperative chemotherapy (PC) only. Patients were enrolled ~1 week before surgery.

REGIMEN

The PPC group was treated preoperatively with 5-FU (320 mg/m²/day) for 5 days CIV and postoperatively with bolus MMC (6 mg/m²) on days 7 and 14 and in months 2, 4 and 6, in conjunction with 6 months of oral 5-FU 200 mg/day beginning 14 days after surgery. The schedule called for preoperative 5-FU CIV administration to be completed on the day before surgery. The PC group received the same postoperative treatment, but the preoperative chemotherapy was omitted.

The dose was reduced or treatment suspended or discontinued on the judgment of the attending physician in the event of serious adverse drug reactions or complications. Use of any other drugs or agents with anticancer action, including anticancer drugs, radiation therapy and immunopotentiating agents, was not permitted, but the use of drugs for symptomatic treatment or for treatment following cancer recurrence was at the discretion of the attending physician.

TREATMENT EVALUATION AND FOLLOW-UP

The primary endpoint of this study was 5 year survival. Secondary endpoints were the 5-year disease-free survival rate (DFS) and adverse reactions. The evaluation of adverse drug reactions was based on published criteria from the Japan Society for Cancer Therapy (10,11).

Follow-up testing was performed yearly for 5 years after surgery in all patients. The primary laboratory tests were performed before surgery and at 2 and 4 weeks and 2, 3, 4 and 6 months after surgery. CEA was measured before enrollment and at 1 month intervals after surgery or each time the patient came to the hospital. The CEA cutoff line was the cutoff value for the method used at the relevant institution. Values below the cutoff line were defined as ‘CEA low’ and values above the cutoff line as ‘CEA high’.

SAMPLE SIZE

The results of our earlier study showed a 5-year DFS of 64.6% in the chemotherapy group for Duke’s stage C colon cancer and rectal cancer patients. Calculations based on the Gehan table (12) indicated that the current study would require 260
Preoperative therapy in colorectal cancer patients (Duke’s stage C, 65%; $\alpha = 0.05$, $\beta = 0.20$; detection of 10% difference).

Because it can be difficult to distinguish Duke’s stage B and C cancers preoperatively, we allowed both Duke’s stage B and C patients to be eligible for enrollment. Based on the above figures and assuming a 1:1 ratio of Duke’s stage B and C patients and an estimation that 10% of patients would be excluded from analysis, we calculated that 1144 patients would be required for this study.

**STATISTICAL ANALYSIS**

We used the $\chi^2$-test, the $U$-test and Student’s $t$-test to check for bias in patients’ characteristics. The Kaplan–Meier method was applied to calculations of survival (13). The overall survival rate was analyzed both on the basis of intent-to-treat (ITT) and per-protocol (PP). The disease-free survival rate was analyzed on the basis of PP. The log-rank test and the generalized Wilcoxon (g-Wilcoxon) test were applied to the duration of survival and disease-free survival. A level of significance was set at $P < 0.05$ (two-sided test). The statistical software used was the SAS System for Windows, Release 6.12 (SAS Institute, Cary, NC).

**RESULTS**

**PATIENT CLASSIFICATION AND CHARACTERISTICS**

A total of 1355 patients from 205 institutions across Japan were enrolled between February 1991 and December 1992. There were 755 cases of colon cancer (PPC 379; PC 376) and 600 cases of rectal cancer (PPC 289; PC 311). ITT analysis was performed on 1277 patients. For colon cancer, 46 patients were ineligible for ITT analysis (non-cancerous lesion, 14; double or multiple cancer, 9; enrollment violations, 8; age violations, 4; other, 11), leaving 709 eligible patients (93.9%). For rectal cancer, 32 patients were ineligible for ITT analysis (non-cancerous lesion, 5; double or multiple cancer, 8; enrollment violations, 7; age violations, 5; other, 7), leaving 568 eligible patients (94.7%). PP analysis was performed on 937 patients. Of the patients included in the ITT analysis set for colon cancer, an additional 44 cases in which the tumor site classification

| Table 1. Patients’ characteristics based on an intent-to-treat (ITT) analysis |
|---------------------------|---------------------------|
|                          | Colon                     | Rectum                    |
|                          | PPC          | PC          | $P$-value | PPC          | PC          | $P$-value |
| N                        | 351          | 358         |           | 272          | 296         |           |
| Gender                   |              |             |           |              |             |           |
| Male                     | 189          | 211         | 0.917*    | 0.746*       |             |           |
| Female                   | 162          | 147         |           |              |             |           |
| Mean age ± SD (years)    | 57.1 ± 8.5   | 57.8 ± 8.5  |           | 57.1 ± 8.1   | 56.8 ± 8.3  |           |
| CEA†                     | 0.850*       |             |           | 0.539*       |             |           |
| Low                      | 203          | 205         |           | 151          | 167         |           |
| High                     | 118          | 118         |           | 99           | 112         |           |
| Unknown                  | 30           | 35          |           | 22           | 17          |           |
| Resection curability‡     | 0.012*       |             |           | 0.934*       |             |           |
| Curative                 | 322          | 307         |           | 245          | 266         |           |
| Non-curative             | 29           | 51          |           | 27           | 30          |           |
| Grade of differentiation | 0.035*       |             |           | 0.716*       |             |           |
| Well                     | 170          | 197         |           | 127          | 141         |           |
| Moderate                 | 156          | 144         |           | 122          | 136         |           |
| Poor                     | 16           | 4           |           | 5            | 7           |           |
| Mucinous                 | 7            | 10          |           | 11           | 8           |           |
| Other                    | 2            | 3           |           | 7            | 4           |           |
| Duke’s classification    |              |             | 0.456†    | 0.234‡       |             |           |
| Duke’s A                 | 33           | 33          |           | 51           | 41          |           |
| Duke’s B                 | 143          | 171         |           | 91           | 103         |           |
| Duke’s C                 | 148          | 108         |           | 111          | 130         |           |
| Duke’s D                 | 27           | 46          |           | 19           | 22          |           |

*$\chi^2$-test. †CEA low, below CEA cutoff value; CEA high, above CEA cutoff value. ‡Curative, complete removal of tumor with histologically clear margin and removal of nodal metastases; non-curative, all others. §$U$-test.
tion at enrollment did not agree with the surgical findings and 135 cases who were ineligible for PP analysis (Duke's stage A, 60; non-curative resection, 73; death, 2) were excluded, leaving 530 eligible patients (70.2%). Of the patients included in the ITT analysis set for rectal cancer, an additional 12 cases in which the tumor site classification at enrollment did not agree with the surgical findings and 149 cases who were ineligible for PP analysis (Duke's stage A, 91; noncurative resection, 57; death, 1) were excluded, leaving 407 eligible patients (67.8%). The 5-year follow-up rate was 96.8% (1312/1355), with 43 patients lost to follow-up.

Table 1 summarizes the patients' characteristics for the ITT analysis set. For colon cancer, bias was noted between the two groups with regard to both gross curability and histological typing ($P < 0.05$). No bias was noted with regard to any other patient characteristic. In the rectal cancer group, no significant bias was observed between the two groups.

**FIVE-YEAR SURVIVAL**

ITT analysis showed 5-year survival rates for colon cancer 77.3% in the PPC group and 75.7% in the PC group and for rectal cancer 67.2% and 69.2%, respectively, indicating no significant difference between the two treatment groups for either disease (Fig. 1). The ITT analysis set showed a significantly greater number of cases of non-curative resection among colon cancer patients in the PC group ($P < 0.05$), but even after adjusting for this factor, there was no significant difference in the 5-year survival rate.

PP analysis showed 5-year survival rates for colon cancer 82.0% in the PPC group and 83.9% in the PC group and for rectal cancer 66.8% and 72.8%, respectively, again with no significant difference between the groups for either treatment regimen or disease. Results of the 5-year survival rate were nearly identical for ITT analysis and PP analysis.
FIVE-YEAR DFS AND RECURRENCE

PP analysis showed 5-year DFS for colon cancer 76.0% in the PPC group and 80.7% in the PC group and for rectal cancer 60.5% and 63.0%, respectively (Fig. 2), indicating no significant differences. Recurrent disease during the 5 years after surgery was confirmed for colon cancer in 72 patients in the PPC group and 59 patients in the PC group and for rectal cancer in 93 and 106 patients, respectively. Initial recurrence most commonly involved the liver in colon cancer (PPC 9.5%, PC 9.4%), followed by the lungs (PPC 6.4%, PC 4.1%). Local recurrence was more common in rectal cancer (PPC 13.3%, PC 16.4%), with a similar incidence of metastasis to the liver and lungs (PPC 12.8%, PC 11.0%). No bias was noted between the two groups regarding the incidence of these recurrences.

TREATMENT COMPLIANCE

The 5-FU CIV treatment completion rate in the PPC group was high for patients with both colon cancer (97.0%) and rectal cancer (96.8%). The MMC completion rate for colon cancer was 75.8% in the PPC group and 67.3% in the PC group and for rectal cancer 72.3% and 71.2%, respectively. Full compliance (80% or better) of oral 5-FU was achieved in 81.8% of colon cancer patients in the PPC group and 84.6% in the PC group and in 84.6% of rectal cancer patients in the PPC group and 81.8% in the PC group. No statistically significant difference in postoperative chemotherapy compliance was noted between the two groups.

ADVERSE REACTIONS

Five out of 1355 enrolled patients (0.36%) died within one postoperative month and two of the dead patients were assessed as absolutely non-curative resection. All these five patients were analyzed by ITT. Three of them in the PC group all completed preoperative chemotherapy without adverse reactions, etc.

Table 2 shows a comparison of adverse reactions based on PP analysis between the PPC group and the PC group. The most common of these was leukopenia, which occurred at grade 2 or above in 24.1% (105/435) of the PPC group and 19.6% (90/460) of the PC group. Grade 4 adverse drug reactions developed in two patients in the PPC group (one case of thrombocytopenia and one case of diarrhea), but were ameliorated by withdrawal of treatment. No significant differences in the incidence of adverse drug reactions, including grade 4 reactions, were noted between these treatment groups and no effects of preoperative chemotherapy on postoperative complications were noted.

DISCUSSION

We performed a multicenter randomized comparative study enrolling 1355 patients from 205 hospitals across Japan. This
was not only a large pool of patients but also a highly reliable institutional group, since over half of the participating institutions are major hospitals at the cutting edge of colorectal cancer treatment in Japan.

The selection of participating patients was difficult because of the necessity to make the selection before surgery on the basis of limited information. As a result, only 70.2% of colon cancer patients and 67.8% of rectal cancer patients were actually eligible for PP analysis. PP analysis showed a 5-year survival rate in the PC group (active control) of 83.9% in colon cancer patients and 72.8% in rectal cancer patients, almost identical with our earlier findings under the same treatment regimen (colon cancer 82.1%, rectal cancer 73.6%) (2–4). These results demonstrated the reproducibility of our findings regarding the clinical effectiveness of postoperative MMC and oral 5-FU.

However, this study failed to prove the efficacy of preoperative chemotherapy, which was its primary objective. Overall analysis showed no improvement in therapeutic effectiveness or in DFS as a result of preoperative chemotherapy in either colon cancer or rectal cancer patients. A study of preoperative chemotherapy with carmoful (an oral 5-FU prodrug) in patients scheduled for curative colorectal resection was being performed in Japan at about the same time as the present study. In that study, similarly to our results, preoperative chemotherapy produced no improvement in either overall survival or DFS (14).

It is possible that these negative results occurred because the dose used in this protocol was too low and that we should reconsider the protocol structure. However, it should be possible to obtain satisfactory effects even when using a low-intensity dose protocol if the protocol is applied only to patients who are highly sensitive to the relevant anticancer drug. A recent report suggests that it may be possible actually to predict 5-FU responders in advance by measuring the mRNA for 5-FU-metabolizing enzymes within the tumor (15).

We investigated histological effects of preoperative chemotherapy in patients from the Department of Surgery II and the Department of Gastrointestinal Surgery of Tokyo Women’s Medical University who were enrolled in the present study (chemotherapy group, n = 15; non-chemotherapy group, n = 16; data not shown). We found slight histological degeneration in the chemotherapy group, although there was no clear evidence of down-staging. It is possible that in pronounced cases of such histological degeneration, there might be additional life-prolonging effects from postoperative chemotherapy. When Fujii and colleagues treated patients scheduled for colorectal cancer resection with 600 mg of oral UFT (tegafur and uracil) for 10 days before surgery, they found that survival was improved by postoperative chemotherapy in those patients who showed a histological response to the preoperative treatment (16). Nakajima et al. reported an insignificant increase in the general survival rate among histological responders in comparison with non-responders (17). These reports involved small numbers of patients and scant evidence. However, it appears that although preoperative chemotherapy does not produce an obvious down-staging effect, this treatment may damage tumor tissue to some extent and thus contribute to the effectiveness of postoperative chemotherapy.

Our research group is now exploring the potential benefits of a protocol that combines 5-FU CIV treatment immediately after surgery with basic postoperative MMC by protracted intravenous infusion and oral 5-FU. Some patients are now in their third year after surgery and we are able to provide an interim report. Our findings to date indicate a significantly higher 3-year survival rate in the group treated immediately after surgery with 5-FU CIV than in the active control group treated only with postoperative MMC by protracted intravenous infusion and oral 5-FU (92.4% vs 81.6%, P = 0.023) and we hope that this protocol will contribute to extending survival in cancer patients (18).

APPENDIX

COOPERATIVE STUDY GROUP INVESTIGATORS

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