The Benefit of Post-Operative Adjuvant Chemotherapy Using Oral Fluoropyrimidines in Rectal Cancer

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Summary: Recent meta-analysis has shown that oral fluoropyrimidines is effective as post-operative adjuvant therapy in stage II or III colorectal cancer. However, because the efficacy of oral fluoropyrimidines was expected to be mild, it is important to know patients who respond to this mild chemotherapy for reasonable adjuvant therapy for rectal cancer. To clarify the benefit and problems of the post-operative adjuvant chemotherapy using oral fluoropyrimidines, the clinicopathological data of 169 rectal cancer patients treated with or without the post-operative chemotherapy were analyzed retrospectively. Patients in chemotherapy group (n=100) underwent curative resection with lymphadenectomy were followed by administration of oral fluoropyrimidine. Other 69 patients underwent surgery alone. The disease-free survival rates were compared between the two groups. The disease-free survival rate in the chemotherapy group was significantly higher than that in the surgery alone. However, no significant difference in disease-free survival rate was found for those with tumor which was associated with metastasis of mesenteric lymph node or node belonging to the internal iliac artery, and tumor with lymphatic invasion or venous invasion. Post-operative adjuvant chemotherapy using oral fluoropyrimidines such as UFT and 5'-DFUR might not reduce the risk of recurrence in rectal cancer with metastasis of mesenteric lymph node or node belonging to the internal iliac artery, and with lymphatic permeation and venous invasion.

Key words post-operative adjuvant chemotherapy, oral fluoropyrimidine, rectal carcinoma, mesenteric lymph node metastasis, metastasis of node belonging to the internal iliac artery, lymphatic permeation, venous invasion

INTRODUCTION

Colorectal cancers remain one of the leading killers in the world. The mainstay for treatment of colorectal cancer with curative intent is surgical resection. In node-positive or stage III patients, surgery alone offers cure to roughly half of patients treated [1]. Thus, addressing the high risk of recurrence necessarily involves the use of systemic agents, chemotherapy, or immunotherapy after surgical removal of primary disease. In worldwide, infusion 5-fluorouracil (5-FU) plus leucovorin combination
therapy (5-FU/LV) was thought to be standard for stage III colon cancer for the past decade [2].

In Japan, since the 1980s, oral 5-FU derivatives (oral fluoropyrimidines) such as UFT (1: tegafur + 4: uracil) and 5'-DFUR, an intermediate of capecitabine, have mainly been used as post-operative adjuvant chemotherapy for colorectal cancer. A recent meta-analysis reported that oral fluoropyrimidines are more useful in patients with colorectal cancer at stage II or III than in those treated with surgery alone [3,4]. We have employed the post-operative adjuvant chemotherapy using oral fluoropyrimidine for stage II or III rectal cancer. However, the efficacy of the post-operative adjuvant chemotherapy using oral fluoropyrimidines was expected to be mild, because the dosage setting of the therapy was low to make adverse effects not severe. Thus, it is important to know which patients are sensitive to oral fluoropyrimidines for application of more intensive chemotherapies. In the present study, to clarify patients who respond to this mild post-operative adjuvant chemotherapy using oral fluoropyrimidines, the clinicopathological data of patients treated with or without the post-operative chemotherapy were reviewed retrospectively.

MATERIALS AND METHODS

A total of 169 patients enrolled the analysis. Eligible criteria of the study were pathological stage II or III rectal cancer according to the UICC classification [5]. The patients were underwent potentially curative resection with lymphadenectomy between 1988 and 1998, and received no preoperative chemotherapy, immunotherapy and radiotherapy. When the distal margin of tumor located below the peritoneal reflection, dissection of pelvic lymph node belonging to the iliac artery was performed. Post-operative adjuvant chemotherapy was performed in 100 patients (Chemotherapy Group). Other 69 patients underwent surgery alone (Surgery Alone). Fluoropyrimidine such as UFT and 5'-DUUR was administered orally for longer than 6 months. The duration of chemotherapy in most patients was 1 year. The chemotherapy started from 2 to 4 weeks after surgery. The usual oral dosage was 500 mg/m²/day in 5'-DFUR, 250 mg/m²/day in UFT. The main reasons for surgery alone were high age, severe complications such as heart disease and renal disease, and patient’s refusal.

Follow-up investigations were performed through outpatient visits, by letter, or by telephone, and the most recent date of contact for each patient was regarded as the final date of confirmation. The most recent date was the last day of December 2003. The median follow-up period was 60 months in the Surgery Alone and 87 months in the Chemotherapy Group. The presence or absence of any recurrence was determined by barium enema, digital examination, measurement of serum tumor marker carcinoembryonic antigen (CEA) level, and/or by findings on chest radiography, ultrasonography (US), computed tomography (CT), or magnetic resonance imaging (MRI).

The incidence and the mode of recurrence, and survival rate and disease-free survival rate prepared by Kaplan-Meier method, were compared between the Chemotherapy Group and the Surgery Alone, as the control. Multivariate analysis for the factors related with disease-free survival was also carried out.

Statistical analysis

All data were compiled and analyzed by Statistical Analysis Software (SAS) version 6.12, (SAS institute, Cary, NC, USA). The statistically significant difference in clinicopathological characteristics between groups was assessed with the χ² test, Fisher’s exact test, and student’s t test. Differences between groups in Kaplan-Meier plots were evaluated using the log-rank test. Major prognostic factors were incorporated into a multivariate analysis model for stepwise analysis. These factors underwent regression analysis to calculate risk ratios.

RESULTS

The background of the patients was summarized in Table 1. The average age in the Surgery Alone was significantly higher than that in the Chemotherapy Group. However, there was no significant difference in sex, distribution of the tumor stage, tumor depth, and tumor histology between the two groups. The incidence of recurrence was 39% in the Surgery Alone and 25% in the Chemotherapy Group, respectively. There was a statistical significant difference (p=0.043). However, no difference in the pattern of recurrence was found between the groups. The overall survival rate and disease-free survival rate in the Chemotherapy Group were significantly higher than those in the Surgery Alone (Fig. 1).

Various factors such as post-operative adjuvant chemotherapy, histological tumor grade (well vs. others), tumor infiltration (T4 vs. others), lymph
TABLE 1. The background of the patients

<table>
<thead>
<tr>
<th></th>
<th>Age* (mean±sd)</th>
<th>Sex (M/F)</th>
<th>Stage (II/III)</th>
<th>T-factor (T1-3/T4)</th>
<th>Histology (well/others)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery Alone</td>
<td>69.4±13.2</td>
<td>40/29</td>
<td>30/39</td>
<td>61/8</td>
<td>48/21</td>
</tr>
<tr>
<td>(n=69)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>60.3±11.3</td>
<td>72/28</td>
<td>38/62</td>
<td>96/4</td>
<td>69/31</td>
</tr>
<tr>
<td>(n=100)</td>
<td></td>
<td></td>
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</table>

*: p<0.001

A

Chemotherapy (n=100)  
Surgery Alone (n=68)  
p=0.012 (log-rank)

B

Chemotherapy (n=100)  
Surgery Alone (n=69)  
p=0.004 (log-rank)

Fig. 1. Disease-free survival curves based on the chemotherapy. A, Disease-free survival curves. B, Overall survival curves.

node metastasis (− vs. +) (metastasis of the mesenteric lymph node or node belonging to the internal iliac vessel vs. none), lymphatic permeation (ly− vs. ly+) [6] and venous invasion (v− vs. v+) [7], age, and sex were evaluated for their independent contributions to the disease-free survival rates after operation using Cox’s proportional hazards model. The analysis indicated that the mild post-operative adjuvant chemotherapy was a significant prognostic factor in addition to the lymph node metastasis, and the venous invasion (Table 2).

When the disease-free survival rates were stratified according to the tumor stage, the disease-free survival rate in Chemotherapy Group was significantly higher than that in the Surgery Alone in stage III cancer, whereas no significant difference was found between the two groups in stage II cancer (Fig. 2). In the patients with only pararectal lymph node metastasis or without the metastasis, the disease-free survival rates in the Chemotherapy Group were significantly higher, however, in the patients with metastasis of the mesenteric lymph node or node belonging to the internal iliac artery, the disease-free survival rates were similar between the Chemotherapy Group and the Surgery Alone (Fig. 3).

When the disease-free survival rate was stratified according to the presence or absence of lymphatic permeation, the significant difference in disease-free survival rate between the Chemotherapy Group and the Surgery Alone was found in the patients with no lymphatic permeation, but not in the patients with the lymphatic permeation (Fig. 4). As well as the lymphatic permeation, the similar result was found when stratified according to the venous invasion (Fig. 5).
Table 2.

Multivariate analysis for disease-free survival time

<table>
<thead>
<tr>
<th>Factor</th>
<th>p value</th>
<th>95% CI</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy (−) vs. (+)</td>
<td>0.003</td>
<td>1.283-3.852</td>
<td>2.293</td>
</tr>
<tr>
<td>LN metastasis (+) vs. (−)</td>
<td>0.009</td>
<td>1.276-4.525</td>
<td>2.331</td>
</tr>
<tr>
<td>Venous invasion v2 vs. v0-1</td>
<td>0.034</td>
<td>1.011-3.040</td>
<td>1.825</td>
</tr>
</tbody>
</table>

LN: lymph node
The grading of venous invasion (v) was defined as our previous report [7].

Fig. 2. Disease-free survival curves stratified according to the tumor stage. A, Stage II. B, Stage III.

Fig. 3. Disease-free survival curves in patients stratified according to presence or absence of metastasis of the mesenteric lymph node or node belonging to the internal iliac artery.

LN: lymph node. A, No or only pararectal LN metastasis. B, Mesenteric or internal iliac LN metastasis.
DISCUSSION

Since the 1990s, intravenous 5-FU/LV therapy was introduced worldwide as the standard post-operative adjuvant chemotherapy for colon cancer [2]. In particular, the significant survival benefit for the 5-FU/LV after a curative resection for node-positive or stage III colon cancer has been established, whereas the current evidence does not support the adjuvant chemotherapy for all patients with stage II colon cancer [8,9] and for rectal cancer. Recently, oral 5-FU derivative capecitabine which has similar anti-tumor efficacy to intravenous 5-FU/LV for advanced colorectal cancer [10], has been investigated to determine effective in post-operative adjuvant therapy for colorectal cancer [11]. In general, the chemotherapy using oral fluoropyrimidines, when comparing to that of either 5-FU/LV, irinotecan [12], oxaliplatin [13] or their combinations [14,15], was characterized by a lower incidence of adverse effects, especially infrequent adverse effects of grade 3 or higher [16]. This is a reason that the chemotherapy using oral fluoropyrimidines can be continued on an outpatient basis without decreasing quality of life. For patients, these are critical benefits of the therapy using oral fluoropyrimidines.
Recent meta-analyses reported that post-operative oral fluoropyrimidines are more useful in patients with colorectal cancer than in those treated with surgery alone [3,4]. In our study, the comparison of overall survival rate, disease-free survival rate and the multivariate analysis supported the efficacy of the post-operative adjuvant chemotherapy using oral fluoropyrimidines for stage II or III rectal cancer. However, anti-tumor effects of the mild chemotherapy using oral fluoropyrimidines are thought to be less than the intensive chemotherapy using either infusion 5-FU/LV, irinotecan, oxaliplatin or their combinations. It has been shown that the more intensive post-operative adjuvant chemotherapy, FOLFOX 4 (oxaliplatin + 5-FU/LV), showed higher efficacy compared to 5-FU/LV in stage III colon cancer [17]. Our question is whether post-operative oral fluoropyrimidine using UFT or 5'-DFUR is effective for all stage II or III rectal cancer. The meta-analysis [4] indicated that the risk reduction of oral fluoropyrimidines for disease-free survival and overall survival was higher in the early stages, Dukes’ A or Dukes’ B, rather than in Dukes’ C in colorectal cancers. This suggested that oral fluoropyrimidines might be ineffective for patients with highly lymphatic spreading tumor. Our data indicated that the mild adjuvant chemotherapy using oral fluoropyrimidines reduced the risk of recurrence and improved the disease-free survival rate after surgery in stage III rectal cancer, but the adjuvant chemotherapy failed to demonstrate any significant survival benefit in patients associated with metastasis of the mesenteric lymph node (intermediate node, principal node) and/or node belonging to the internal iliac artery. These results suggested that the mild post-operative chemotherapy using oral fluoropyrimidines might not be enough to reduce the risk of recurrence in rectal cancer patients with involvement of the mesenteric lymph node and/or node belonging to the internal iliac artery.

Of another interest, in the tumors with lymphatic permeation and/or venous invasion the adjuvant chemotherapy could not reduce the risk of recurrence and could not improve the disease-free survival. These results also suggested that post-operative oral fluoropyrimidines was not enough to reduce the risk of recurrence in biologically aggressive tumors. Although our data did not support the adjuvant chemotherapy for all patients with stage II rectal cancer, in biologically aggressive stage II rectal cancer post-operative adjuvant chemotherapy should be considered. Also the results indicated that more intensive chemotherapy rather than oral fluoropyrimidines should be applied for such patients.

In conclusion, post-operative adjuvant chemotherapy using oral fluoropyrimidines such as UFT and 5'-DFUR might reduce the risk of recurrence in stage II or III rectal cancer, but the procedure was insufficient for those with metastasis of mesenteric lymph node or node belonging to the internal iliac artery or with a biologically aggressive tumor. Thus, more intensive chemotherapy using infusion 5-FU/LV, oral UFT/LV, new generation of oral fluoropyrimidine such as capcitabine, irinotecan, oxaliplatin or their combinations should be considered for such patients.

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REFERENCES


