Abstract. **Aim:** To assess the practical efficacy of low-dose leucovorin plus 5-fluorouracil (LV/5-FU) in elderly patients with metastatic colorectal cancer. **Patients and Methods:** The records of 20 patients treated with LV/5-FU for unresectable metastatic disease from colorectal cancer from 1999 to 2004 were retrospectively reviewed. The patients received LV/5-FU as first-line, and low-dose CPT-11 and CDDP regimen (CPT-11/CDDP) as second-line therapy. **Results:** In the treatment of LV/5-FU, no patients had CR, 3 patients had PR, 4 patients had SD and 13 patients had PD, which results in a response rate (RR) of 15% and in a disease control rate (DCR) of 35%. MST of all patients was 18.4 months. There was one patient who experienced grade 3 or 4 adverse reactions during the course of these regimens. **Conclusion:** Low-dose LV/5-FU chemotherapy in elderly patients with metastatic colorectal cancer could be acceptable in order to avoid adverse effects and to obtain quite a favorable survival time.

Chemotherapy has an important role in the management of colorectal cancer. 5-Fluorouracil (5-FU)-based adjuvant chemotherapy has resulted in increased disease-free and overall survivals in stage III colon cancer (1) and palliative chemotherapy has extended the lives of patients with metastatic colorectal cancer and improved the quality of life compared with best supportive care (2). Recent additions to the chemotherapy armamentarium for this disease have begun to prolong median survival times (3-5). In trials in which patients are exposed to all three approved chemotherapy agents, oxaliplatin, irinotecan and 5-FU/LV, or capecitabine during the course of their disease, median survival has reached 20 months (6). Current standard first-line regimens for metastatic colorectal cancer are FOLFOX (infusional 5-FU/LV with oxaliplatin) and FOLFIRI (infusional 5-FU/LV with irinotecan) (7). The addition of bevacizumab to a two-drug regimen (irinotecan with 5-FU/LV) prolongs median survival to 20 months, with an increased amount of additional toxicity (8). In older patients, the importance that the chosen regimen has an acceptable toxicity profile is accentuated because such individuals may not be as robust as their younger counterparts, and because they may place a different value on the time and logistical challenges relevant to a course of treatment.

Low-dose chemotherapy has been performed for unresectable cancer under the concept of tumor dormancy therapy. Low-dose LV/5-FU and low-dose CPT-11/CDDP for recurrent or metastatic colorectal cancer have been reported to provide favorable survival without toxicity (9, 10). In the present study, we performed low-dose LV/5-FU as first-line therapy for elderly patients (over 75 years old) with unresectable metastasis from colorectal cancer and reported the results of low-dose chemotherapy.

**Patients and Methods**

**Patients.** The records of twenty patients treated with low-dose chemotherapy for unresectable metastasis from colorectal cancer at the Department of Surgery, Tokyo Women's Medical University, Medical Center East between 1999 and 2004 were retrospectively reviewed. No patients had previously been treated with radiotherapy. Low-dose chemotherapy was performed for the patients with any
A performance status grade. Adequate hematological function (total leukocyte count >3000/µl and platelet count >80000/µl), renal function (serum creatinine <1.5 mg/ml), and hepatobiliary function (total serum bilirubin <1.5 mg/ml) were also essential.

Chemotherapy regimen. The chemotherapeutic administration schedules of the low-dose leucovorin and 5-FU were according to the modified Mayo Clinic regimen (11-14). Patients were given LV at 20 mg/m² immediately followed by 5-FU at 370 mg/m² by rapid systemic intravenous infusion daily for 5 consecutive days with courses repeated at 4 weeks, 8 weeks and 5 weeks thereafter; or given LV at 20 mg/m² immediately followed by 5-FU at 370 mg/m² as a 2-hour infusion weekly for 5 weeks as one cycle, repeated every week until progressive disease was recognized. If progressive disease was detected by evaluation, patients were given the option of switching to second-line chemotherapy, with a low-dose CPT-11 and CDDP regime (CPT-11 and CDDP were administered on days 1, 8 and 15 every 4 weeks as one cycle). CPT-11 at 27 mg/m² was dissolved in 500 ml 5% glucose and infused intravenously over 120 min. Subsequently, CDDP at 6 mg/m² was dissolved in 100 ml saline and infused for 30 min) (10). During chemotherapy, to avoid vomiting, ondasetron and dexamethasone were administered (15). When toxicities were noted, administrations were delayed or the dose was reduced.

Evaluation. The tumor response was evaluated based on changes in the size of measurable lesions, assessed using CT scans. Assessment of tumor response and toxicities was classified in accordance with RECIST criteria (16) and Common Terminology Criteria for Adverse Events v3.0 (17). In brief, complete response (CR) the disappearance of all target lesions; partial response (PR) at least a 30% decrease in the sum of the longest diameters of target lesions, taking as reference the baseline sum of the longest diameters; progressive disease (PD) at least a 20% increase in the sum of the longest diameters of target lesions, taking as reference the smallest sum of the longest diameters recorded since the treatment started or the appearance of one or more new lesions; stable disease (SD) neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum of the longest diameters since the treatment started.

The survival times in this study were calculated from the initiation of low-dose LV/5-FU using Kaplan-Meier methods.

Results

Patient characteristics. Patient characteristics were as follows. The average age of patients was 77.1 years (range, 75-87 years). Seventeen patients were PS 0, three patients were PS 1.

The sites of metastatic lesion were 12 cases in the liver, 3 in the local peritoneum, 3 in lymph nodes and 3 in the lungs. The median number of cycles given with low-dose LV/5-FU were 5.5 (range, 2-25). Second-line therapy with low-dose CPT-11/CDDP was performed for 11 patients.

Response and overall survival. The response among the 20 patients treated with LV/5-FU is shown in Table I. The MST of all patients was 18.4 months (Figure 1).

Toxicity. The adverse reactions to LV/5-FU are summarized in Table II. There was one patient with grade 3 neutropenia. The most frequent adverse reaction was anorexia. Twelve patients experienced no adverse reactions.

Discussion

In recent years, chemotherapy for advanced colorectal cancer has progressed. In the treatment, infusional LV/5-FU, irinotecan and oxaliplatin must be administered with bevacizumab to prolong survival. Although recent analysis has shown FOLFOX4 maintains its efficacy and safety ratio.
in selected elderly patients with colorectal cancer (18), these regimens are not always tolerable for all patients due to severe toxicities and patients' age (19, 20). Recently, although Kim et al. reported that dose-reduced FOLFOX4 for patients older than 70 years with advanced colorectal cancer as first-line therapy was well tolerated with acceptable toxicity, and provided a benefit with a 35% response rate (21), further observation will be needed to confirm that this regimen can provide clinical benefits for elderly patients. Of course, the suitability of such a dose-reduced regimen should be investigated for individual patients because anticancer drugs may have highly suppressive effects on the host, and frequently cause host immunosuppression (22-25).

Low-dose chemotherapy has been performed under the concept of tumor dormancy therapy (26). Although the response rate might be low, low-dose chemotherapy with LV/5-FU does not have severe adverse effects. Long-term treatment can be possible, obtaining longer median survival times as a result. Ito et al. reported that serial exchange of low-dose 5-FU-based chemotherapy in colorectal carcinoma can induce prolonged cytostastic tumor dormancy (27). Moreover, a recent report indicated that there is an improvement in host immunity with low-dose LV/5-FU treatment (28). Low-dose LV/5-FU treatment should be considered for elderly patients with unresectable metastasis from colorectal cancer from the point of view maintaining host immunity during chemotherapy.

The benefit of second-line chemotherapy with a single administration of irinotecan for colorectal cancer was demonstrated by Cunningham et al. (29). This phase III trial showed that patients treated with irinotecan experienced significantly longer survival than those receiving best supporting care alone. However, 22% of patients experienced grade 3-4 neutropenia and grade 3-4 diarrhea, with a 14% incidence of grade 3-4 vomiting. Currently, like LV/5-FU, even a very low dose of CPT-11 (27 mg/m²) plus CDDP (6 mg/m²) results in prolonged SD without toxicities (10).

In the current study, under these concepts, we chose these low-dose regimens for patients older than 75 years of age. Our data showed that these low-dose regimens could not provide a cure, but would obtain relatively prolonged survival without toxicities. The results suggest that low-dose LV/5-FU for metastatic colorectal cancer should be considered as a first-line therapy.

References


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