LETTER TO THE EDITOR

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Metronomic chemotherapy with capecitabine for metastatic colorectal cancer in very elderly patients

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To the Editor,

The incidence of cancer in elderly patients has increased with prolongation of life expectancy. Despite of advance in the treatment of colorectal cancer (CRC), frail elderly patients with advanced stage still tend to be very reluctant to systemic treatment due to concern about the toxicity following chemotherapy. The main purpose of the systemic chemotherapy for metastatic CRC is palliation to extend overall survival (OS) with improvement in quality of life (QOL). Systemic treatment which is less toxic as well as not inferior in efficacy compared with conventional treatment is highly required for the vulnerable elderly patients. Oral chemotherapeutic agent is more convenient and can be administered at outpatient clinic. Metronomic chemotherapy, continuously low dose administration of chemotherapeutic agents, has been reported to have a low toxicity and anticancer effect. Recently we experienced three very elderly CRC patients who showed durable response and tolerability to metronomic chemotherapy with oral capecitabine at outpatient clinic. Any patient did not show impairment of life quality except one patient who experienced one week of treatment interruption due to grade 1 hand foot syndrome (HFS). Any patient did not experience hematologic toxicity more than grade 2.

Case 1

A 90-year-old male patient presented at our department for the evaluation of 5.0 × 4.4 cm sized lung mass which was incidentally identified on medical examination. He had a 7 years prior history of anterior resection for colon cancer of unknown stage, at another institution. Pathologic examination of the lung mass was suggestive of recurrent metastatic colon cancer (CK20, +; CDX-2, +; CK7, –; TTF-1, –; KRAS mutation, –). Low dose capecitabine (500 mg thrice daily without interruption) was administered according to his age and comorbidity (hypertension and depression). Three months later, follow-up computed tomography (CT) showed partial regression of the lung mass (4.4 × 5.0 to > 2.7 × 4.0 cm) (Fig. 1A and 1B; arrows). Subsequently, his response was maintained for 12 months, and he remained in good condition. Leukopenia or thrombocytopenia was not observed throughout chemotherapy with low dose capecitabine. After confirmation of progression, the regimen was switched to combination chemotherapy with cetuximab and irinotecan, as the second line treatment. Although modest response was observed on the

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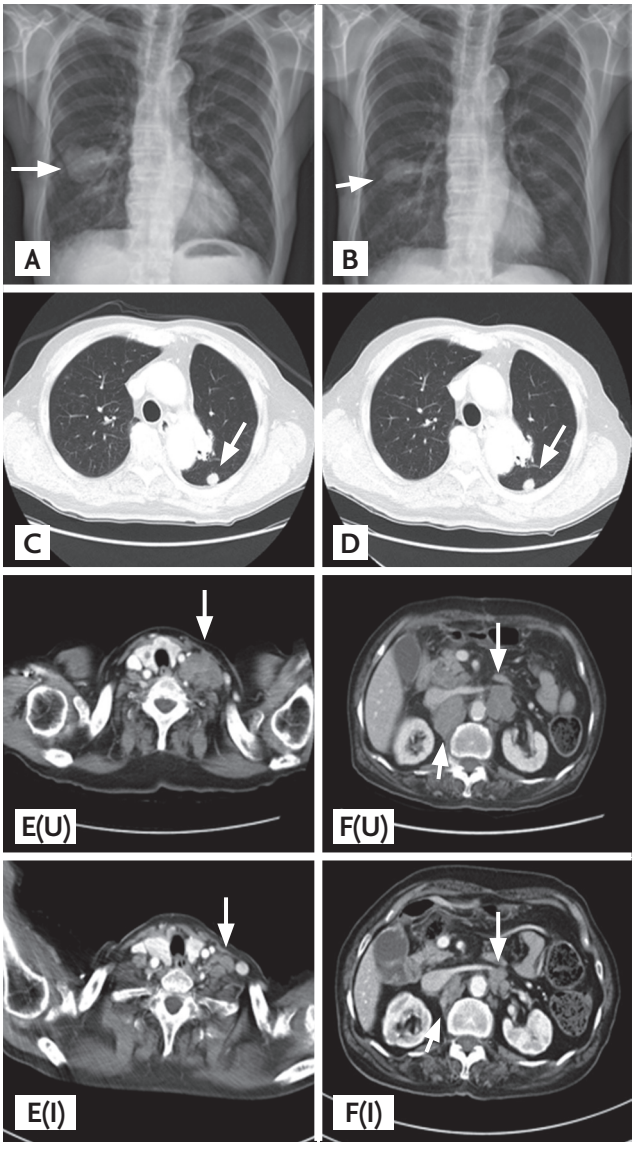

Figure 1. (A, B) Chest posteroanterior shows 5 cm-sized irregular mass (arrows) on right middle lobe (A). The mass much regressed after 3 months of capecitabine treatment (B). (C, D) Chest computed tomography (CT) shows no remarkable change of metastatic nodule (arrows) in left lower lobe superior segment. (E, F) Chest CT shows enlarged metastatic nodule (arrow) in left supraclavicular region (upper panel of E) and abdomen CT shows multiple metastatic lymphadenopathy (arrow) in portocaval, left para-aortic and aortocaval area (lower panel of E). After 3 months of capecitabine treatment, metastatic lymphadenopathy of the same lesion was much regressed (F).

chest CT at 8 weeks posttreatment, he complained of fatigue, diarrhea, loss of appetite, and worsening QOL, and requested interruption of the treatment.

Case 2

An 89-year-old male patient was referred for the management of recurrent metastatic colon cancer. On past history, he had undergone operation and adjuvant 5-fluorouracil (5-FU)/leucovorin chemotherapy for colon cancer at another institution, 6 years prior. Nine months ago, he received left upper lobectomy for lung mass. Recurrent metastatic colon cancer was suspected on pathologic examination of the lung mass (CK7, –; TTF-1, –; CDX-2, +; KRAS mutation, –). Nine months after surgical resection, another lung nodule was newly identified. Therefore he was referred to our department and treated with low dose capecitabine (500 mg thrice daily without interruption). Follow-up CT 3 months posttreatment, showed minimal increment of lung nodule within the stable disease category (Fig. 1C and 1D; arrows). The patient received additional 2 months of capecitabine monotherapy without treatment related complication, until confirmation of progression. The patient refused further treatment for the progressive disease and is on regular follow-up at the outpatient clinic.

Case 3

An 86-year-old female patient presented at our institution for the management of advanced colon cancer that was identified during routine medical examination. Six years ago, she had received colonoscopic polypectomy for a sigmoid colon polyp, which was confirmed as a well differentiated adenocarcinoma. At the time, she received only regular check-up after polypectomy, since pathologic result and sequential abdomen CT had no evidence of remnant lesion. However, 6 years later, her laboratory findings revealed elevated carbohydrate antigen 19-9 and newly developed anemia. Metastatic colon cancer involving paraaortic, portocaval, and supraclavicular lymph node was confirmed (KRAS mutation, +) on further examination. She then received right hemicolectomy and was referred to our department for systemic chemotherapy. She had been treated for comorbid illnesses, i.e., hypertension, osteoarthritis, anxiety disorder, and old pons infarction. Her performance status (PS) was Eastern Cooperative Oncology Group 2 or 3 at that time. She refused hospitalization. Considering poor PS and old age, low dose capecitabine (500 mg thrice daily uninterrupted) was prescribed. Treatment was well tolerated. Follow-up CT 3 months posttreatment, revealed marked regression of metastatic lymphadenopathy (Fig.

1E and 1F). However, her PS had deteriorated without definite treatment related toxicity and she requested interruption of treatment after another 1.5 months of treatment. Disease progression was identified soon after treatment interruption. Although she experienced grade 1 HFS, there was no treatment related toxicity more than grade 2, until drug interruption. Aspiration pneumonia occurred during supportive home care. Her condition worsened to respiratory failure and she eventually expired of adult respiratory distress syndrome in approximately 3 months of admission

Several novel milestone chemotherapeutic agents over the last 2 decades have significantly improved median OS to approximately 24 months in patients with metastatic CRC. Nonetheless, the choice of the most suitable chemotherapy regimen is still a difficult challenge in elderly patients because of comorbidity and treatment related toxicities. According to previously reported studies on various chemotherapy regimens for metastatic CRC, most of combination chemotherapy regimens did not show distinct survival benefit in elderly patients. Although a few studies demonstrated favorable responses of combination chemotherapy, which is comparable to young patients, in the combination chemotherapy arm of elderly patients, significantly higher hematologic and non-hematologic toxicity were identified [1]. Moreover, there has been a lack of data in patients older than 80 years, because very elderly patients are usually excluded from clinical trials. Consequently in clinical practice, monotherapy has been preferred in the treatment of metastatic CRC patients older than 80 years and 5-FU has been the most frequently prescribed monotherapy agent. However, since capecitabine has been recognized as a reasonable alternative to intravenous 5-FU based on equivalent efficacy and higher tolerability, capecitabine monotherapy has received attention as a plausible first line treatment option [2]. Additionally, an easy administration of capecitabine via oral route gave patients greater flexibility and convenience without interruption of daily life. Capecitabine has been used in various schedules and dosages; however, many clinical trials prescribed 1,000 mg to 1,250 mg/m^2 twice a day for 2 weeks with 1 week of rest, as an initial dose of capecitabine monotherapy [3]. This dosage was applied equally to both young and elderly patients, although dose adjustment was permitted. Naturally, toxicity profiles of previous studies with a capecitabine monotherapy arm, showed a higher incidence of grade 3/4 adverse events, particularly gastrointestinal toxicities and HFS, in patients aged ≥ 70 years, as compared with the overall patient population. Consequently, a significant portion of patients required dose modification or treatment interruption. That is to say, conventional dose and schedule of capecitabine monotherapy was still burdensome in very elderly patients (≥ 80 years old) despite the better response rate.

Metronomic chemotherapy, which is defined daily low dose chemotherapy without interruption, has been known to suppress cancer progression through its anti-angiogenic and immune modulating effect, rather than direct cytotoxicity. The dose and schedule of metronomic chemotherapy using capecitabine have not established yet [4]. However, when oral capecitabine was administered at fixed doses ranging from 1,000 to 2,000 mg daily for the patients with gastrointestinal tract and breast cancer, good tumor control and favorable toxicity profile were reported [5]. Metronomic capecitabine for elderly patients with gastrointestinal cancer were reported also [5]. Especially, its low treatment related toxicity was thought to be suitable for heavily pre-treated patients or elderly patients for whom, combination chemotherapy or even monotherapy is not feasible. According to the reference, we administered metronomic capecitabine at a fixed dose of 1,500 mg daily for the very elderly CRC patients without significant toxicity. Recently metronomic chemotherapy has been investigated in combination with drug repositioning, radiotherapy, targeted therapy, and immunotherapy [4].

In conclusion, metronomic chemotherapy could be an effective and tolerable treatment option for recurrent or metastatic CRC in very elderly patients. Randomized prospective clinical trials are required to determine the optimal dosage and schedule of metronomic chemotherapy using capecitabine for the patients.

Keywords: Administration, metronomic; Capecitabine; Colorectal neoplasms

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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