Case Report
Chronic myelogenous leukemia after postoperative adjuvant S-1 therapy for rectal cancer: a case report

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Abstract: We report a case in which chronic myelogenous leukemia (CML) developed after postoperative adjuvant S-1 therapy for rectal cancer. A 56-year-old man was diagnosed with rectal adenocarcinoma, which was treated with abdominoperineal resection followed by a year of adjuvant S-1 therapy. At 39 postoperative months, he was diagnosed with CML. Although it remains unclear that CML that develops after treatment involving cytotoxic agents is treatment-related, clinicians should be aware of the possibility of CML developing after S-1 therapy.

Keywords: Chronic myelogenous leukemia, rectal cancer, fluoropyrimidine, S-1

Introduction
Advances in surgery and chemotherapy have improved the outcomes of patients with rectal cancer. On the other hand, therapy-related myeloid neoplasms (t-MN) are one of the most important concerns among oncologists/hematologists. Although t-MN that develop after treatment with topoisomerase II inhibitors, alkylators, or ionizing radiation are well documented, there are few reports about t-MN caused by antimetabolite-based treatment. Furthermore, among t-MN the post-cytotoxic therapy incidence of chronic myelogenous leukemia (CML) is lower than those of other types of leukemia. We herein report a case in which CML developed after postoperative adjuvant S-1 therapy for rectal cancer.

Case presentation
A 56-year-old male was referred to our hospital because of melena in July 2008. On admission, a digital rectal examination revealed a palpable mass with an elastic consistency in his rectum. The patient had been a taxi driver for all of his working life, and he had no prior history of exposure to chemicals or radiation. An endoscopic examination revealed an elevated tumor in his rectum, which was pathologically diagnosed as moderately differentiated adenocarcinoma. Computed tomography demonstrated swollen pelvic lymph nodes, but there was no evidence of distal metastases. He underwent abdominoperineal resection and colostomy with lymph node dissection. A pathological examination revealed metastases to four mesorectal lymph nodes; therefore, he was pathologically staged as T3N2M0, stage IIIC according to the Union for International Cancer Control (UICC) classification, 6th edition.

Thereafter, we recommended that the patient should receive postoperative adjuvant chemotherapy involving a platinum-based agent and continuous intravenous fluorouracil; however, he opted for oral chemotherapy instead because of his occupation. Therefore, he was subjected to oral antimetabolite monotherapy involving 80 mg/m² S-1 [tegafur – gimeracil – oteracil] on weeks 1-4 of a 6-week cycle. After 10 courses of S-1 chemotherapy (total dosage: 33600 mg), he underwent surveillance consultations involving computed tomography scans and blood examinations three times per year. His most recent postoperative surveillance consultation, which was performed at 39 months after surgery, did not detect any evidence of
relapse; however, his white blood cell count was increased. Hence, he was referred to the hematology division. A peripheral blood analysis demonstrated a white blood cell count of 14,100/μL including 0.5% myelocytes, 66.5% neutrophils, 12.5% lymphocytes, 2.5% monocytes, 7% eosinophils, and 11% basophils. In addition, his hemoglobin concentration was 13.9 g/dL, and his platelet count was 393,000/μL, and his serum lactate dehydrogenase level was 341 U/L. Bone marrow aspiration revealed a hypercellular bone marrow, but less than 5% of the cells were blasts (Figure 1). Chromosome analysis of his bone marrow cells showed the following karyotype: 46,XY,t(9;22)(q34;q11.2) [20] (Figure 2). In addition, fluorescent in situ hybridization detected BCR/ABL1 fusion signals in 95% of the cells. Thus, a diagnosis of CML (chronic phase) was made.

The patient was started on dasatinib therapy (100 mg/day) in October 2011, but could not continue with the treatment because of uncontrollable and recurrent pleural effusion. He subsequently received second-line nilotinib (600 mg/day), but it also had to be discontinued due to a grade 3 increase in serum bilirubin level. Therefore, imatinib therapy was attempted in August 2012, which eventually achieved a complete cytogenetic response. Thereafter, the patient exhibited a major molecular response, which persisted at over 2 years after the initial diagnosis of CML.

Discussion

The therapeutic outcome of rectal cancer has greatly improved due to recent progress in the fields of surgery, chemotherapy, and supportive care. In the postoperative setting, adjuvant chemotherapy for patients with stage III disease in whom resection is successful is considered to be the standard therapeutic strategy [1]. On the other hand, t-MN are one of the most important late complications of cytotoxic agent-based cancer treatment. t-MN have been independently categorized since the 4th edition of the World Health Organization classification [2]. The most common types of t-MN include acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), and myelodysplastic/myeloproliferative neoplasms, and the post-cytotoxic therapy incidence of CML is markedly lower than those of AML and MDS. Lichtman reviewed the frequency of secondary leukemia in cancer patients that were treated with chemotherapy with or without radiotherapy. As a result, he found that the incidence of secondary leukemia was 0.29% (1,403/485,374) and that the 1,403 secondary leukemia cases included 179 cases of CML (12.8%) [3]. As for the causative treatment, almost all of the patients examined in the review had been treated with radiotherapy; hence, it was suggested that there is no significant association between CML and exposure to chemotherapy alone [3]. Thus, it remains unknown whether CML that develops after chemotherapy alone represents secondary, or as de novo leukemia. However, a causal relationship between chemotherapy and the development of t(9;22)–positive leukemia has been suggested to exist [4]. Recently, progress has been made in analyzing the genetic mutations that cause t-MN [5]. Although secondary CML can not be cytogenetically distinguished from de novo CML at the present time [6], more detailed studies of the genetic factors (other than BCR/ABL1) associated with post-chemotherapy CML are required.

Regarding chemotherapy, the incidence of fluoropyrimidine–related t-MN is markedly lower than those of t-MN arising after treatment with other cytotoxic agents, such as topoisomerase II inhibitors, alkylating agents, or ionizing radiation. In addition, to the best of our knowledge only about 10 cases of post-antimetabolite treatment CML have been reported [7-14]. Furthermore, cases of S-1–related CML are much more rare [9, 11]. S-1 is frequently used to treat gastric carcinoma, especially in Asian countries [15]; however, studies involving various superiority or non-inferiority-based designs...
have recently reported that S-1 is an effective treatment for other carcinomas such as pancreatic cancer, non-small cell lung cancer, or biliary tract cancer [16-18]. Hence, as the number of patients treated with S-1 might increase in future it is important for oncologists/hematologists to be aware that secondary CML can occur as a late toxicity of S-1 treatment.

Disclosure of conflict of interest

None.

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References


Figure 2. G-banded karyogram showing a karyotype of 46,XY,t(9;22)(q34;q11.2).
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