Chronic Myeloid Leukemia following Chemotherapy with 5’-deoxy-5-fluorouridine for Gastric Cancer

Motohiro Tsuzuki, Kousuke Handa, Kiyoko Yamamoto, Akio Hasegawa, Yukiya Yamamoto, Masato Watanabe, Syuichi Mizuta, Fumio Maruyama, Masataka Okamoto, Nobuhiko Emi and Kohji Ezaki

Abstract

We report here a very rare case of chronic myeloid leukemia (CML) following long-term chemotherapy with 5’-deoxy-5-fluorouridine (5’-DFUR) for gastric cancer. A 69-year-old man was diagnosed with the chronic phase of CML. Six years previously, he underwent radical subtotal gastrectomy for gastric cancer, and was subsequently treated with oral anti-metabolite 5’-DFUR as adjuvant chemotherapy for 6 years. He was placed on imatinib therapy, and achieved a major molecular response 10 months after the initiation of therapy. This is the first reported case of therapy-related CML following 5’-DFUR treatment.

Key words: therapy-related leukemia, chronic myeloid leukemia, 5’-deoxy-5-fluorouridine, gastric cancer

(Int Med 47: 1739-1741, 2008)  
(DOI: 10.2169/internalmedicine.47.1072)

Introduction

Second malignant neoplasms are important late appearing complications after chemotherapy and/or radiotherapy in cancer patients. Therapy-related malignancies include acute leukemia, myelodysplastic syndrome (MDS), Hodgkin’s lymphoma, non-Hodgkin’s lymphoma, and solid tumors. On the other hand, chronic myeloid leukemia (CML) as a secondary malignancy has rarely been reported. We present here a patient with CML following 5’-deoxy-5-fluorouridine (5’-DFUR) therapy for gastric cancer.

Case Report

A 69-year-old man was diagnosed as gastric cancer (T2N1, stage II) in August 2000. He underwent subtotal gastrectomy for tumor of the antrum with an en bloc resection of second-echelon lymph nodes in October 2000. Pathological diagnosis of his gastric cancer was tubular adenocarcinoma of the well differentiated type. The peripheral blood (PB) findings then were: hemoglobin 15.2 g/dL; white blood count (WBC) 6.1×10^9/L with 54% neutrophils, 6% eosinocytes, 36% lymphocytes, 4% monocytes; and platelet count 105×10^9/L. He had been placed on adjuvant chemotherapy with oral 5’-DFUR 600 mg daily for six years, because his CA19-9 level had been higher than normal range. He had not undergone any radiotherapy during or after the operation.

He was born in Aichi, Japan. He worked in the forwarding agency from the age of twenty to sixty years old. His family history was nothing particular. He has had diabetes mellitus (DM) without medication since 45 years old. When he was 62 years old, he underwent cholecystectomy for cholecystitis.

He was doing well with no evidence of recurrence of gastric cancer until October 2006, when leukocytosis and thrombocytosis were found, and he was referred to our department in January 2007.

Neither hepatosplenomegaly nor lymphadenopathy was seen. The PB findings were: hemoglobin 14.2 g/dL; WBC 44.9×10^9/L with 1% myeloblasts, 9% myelocytes, 8% metamyelocytes, 65% neutrophils, 2% eosinocytes, 3% basophils, 10% lymphocytes, 1% monocytes; and platelet count 811×10^9/L. The liver and renal functions were normal range. The lactate dehydrogenase (LDH) was 350 U/L (normal range...
The neutrophil alkaline phosphatase (NAP) score was 27 (normal range 150-350). Bone marrow (BM) examination revealed a marked hypercellular marrow with 4.5% myeloblasts, 7.5% promyelocytes, 13.5% eosinophils, 1.5% basophils and 7% erythroblasts. Megakaryocytes were increased in number. Chromosomal analysis of the BM cells revealed that Ph chromosome with 46,XY,t(9 ; 22)(q34 ; q11.2) was positive in all 20 metaphase cells counted. Molecular examination by reverse-transcriptase chain reaction (RT-PCR) analysis of leukocytes from bone morrow at the time of diagnosis was positive for the major bcr-abl fusion gene. The diagnosis of CML in the chronic phase was made. The present case was strongly suspected to have therapy-related leukemia because he was treated with 5´-DFUR for gastric cancer for a long time. The patient has been treated with imatinib mesylate 400 mg daily since February 2007. A major cytogenetic response was achieved after 3 months of therapy, as proven by a negative FISH analysis for the bcr-abl transcript. Major molecular response as proven by RT-PCR was achieved after 10 months of treatment. He continues therapy of imatinib, although he has edema and weight gain as adverse effects of imatinib.

Discussion

The development of secondary malignancies is a serious complication after successful chemotherapy and/or radiotherapy for initial malignancy. Most frequently experienced therapy-related malignancies are hematological malignancies, especially acute myeloid leukemia (AML) or MDS (1). On the other hand, acute lymphoid leukemia and CML are rare. Devereux reported only 9 (2.6%) cases of CML in 339 cases of therapy-related leukemia (TRL) (2).

The anti-tumor agents that have been reported to be related to TRL include alkylating agents, topoisomerase-II inhibitors, anti-metabolites, and others. Information about TRL associated with anti-metabolites is sparse (3). Some reports suggest that 5-fluorouracil (5-FU), tegafur, uracil/tegafur (UFT), and other anti-metabolites also might be leukemogenic (4, 5). The types of TRL associated with anti-metabolites are MDS or AML, the as same as alkylating agents or topoisomerase-II inhibitors. At present, the incidence of anti-metabolite-related TRL is unknown, but it is obviously lower than the proportion of leukemias following treatment with alkylating agents or topoisomerase-II inhibitors. Some anti-metabolites are given not only for patients with malignant diseases, but also for non-malignant conditions such as rheumatoid arthritis, psoriasis, sarcoidosis, and myasthenia gravis (6-8). Therefore, the question of whether anti-metabolites may cause TRL is important, especially for patients with non-malignant diseases which tend to require long-term use of drugs.

The present case is the first reported case of CML following 5´-DFUR treatment. 5´-DFUR is an oral fluoropyrimidines. It is not effective itself but it becomes active only after conversion to 5-FU by pirimidine nucleoside phosphorylase, which is preferentially located in tumor tissues (9). Thus, 5´-DFUR produces a higher level of 5-FU in the tumor site than in the normal counterpart (10).

There are 6 case reports of CML following fluoropyrimidines such as 5-FU and S-1. These cases including our case are summarized in Table 1 (11-16). The median age of the 5 man and 2 woman patients was 60 (range 52-74). The primary malignant diseases are all solid tumors such as gastric cancer, colon cancer, esophageal cancer and breast cancer. Four cases received combination chemotherapy. The interval between the diagnosis of the primary disease and CML varied from 12 months to 96 months.

Therapy-related CML is defined as patients with radiotherapy or chemotherapy for malignant disease or non-malignant disease and patients who underwent allogeneic organ transplantation and subsequently received immunosuppressive therapy. Waller et al reviewed 287 published cases of therapy-related CML in 1999 (17), including 221 patients

<table>
<thead>
<tr>
<th>Age/ gender</th>
<th>Primary disease</th>
<th>Chemotherapy</th>
<th>Interval to CML (months)</th>
<th>Chromosome</th>
<th>Total dose of fluoropyrimidines</th>
<th>Author (year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>52/M</td>
<td>Gastric cancer</td>
<td>5-FU</td>
<td>33</td>
<td>Ph</td>
<td>600g</td>
<td>Ishiyama T et al (1985) (11)</td>
</tr>
<tr>
<td>74/W</td>
<td>Breast cancer</td>
<td>CPA, MTX, 5-FU</td>
<td>84</td>
<td>Ph</td>
<td>12g/m²</td>
<td>Porta C et al (1993) (12)</td>
</tr>
<tr>
<td>60/M</td>
<td>Esophageal cancer</td>
<td>5-FU</td>
<td>48</td>
<td>Ph (minor-bcr)</td>
<td>292g</td>
<td>Nakamura H et al (2000) (13)</td>
</tr>
<tr>
<td>62/M</td>
<td>Colon cancer</td>
<td>CDDP, 5-FU</td>
<td>12</td>
<td>Ph</td>
<td>unknown</td>
<td>Goke Y et al (2002) (14)</td>
</tr>
<tr>
<td>56/W</td>
<td>Gastric cancer</td>
<td>MTX, 5-FU</td>
<td>96</td>
<td>Ph</td>
<td>unknown</td>
<td>Ueno Kawa K et al (2005) (15)</td>
</tr>
<tr>
<td>55/M</td>
<td>Gastric cancer</td>
<td>S-1</td>
<td>37</td>
<td>Ph (Major-bcr)</td>
<td>41.5g</td>
<td>Higuchi M et al (2006) (16)</td>
</tr>
<tr>
<td>69/M</td>
<td>Gastric cancer</td>
<td>5´-DFUR</td>
<td>75</td>
<td>Ph (Major-bcr)</td>
<td>876g</td>
<td>Present case (2008)</td>
</tr>
</tbody>
</table>


119-229). The neutrophil alkaline phosphatase (NAP) score was 27 (normal range 150-350). Bone marrow (BM) examination revealed a marked hypercellular marrow with 4.5% myeloblasts, 7.5% promyelocytes, 13.5% eosinophils, 1.5% basophils and 7% erythroblasts. Megakaryocytes were increased in number. Chromosomal analysis of the BM cells revealed that Ph chromosome with 46,XY,t(9 ; 22)(q34 ; q11.2) was positive in all 20 metaphase cells counted. Molecular examination by reverse-transcriptase chain reaction (RT-PCR) analysis of leukocytes from bone morrow at the time of diagnosis was positive for the major bcr-abl fusion gene. The diagnosis of CML in the chronic phase was made. The present case was strongly suspected to have therapy-related leukemia because he was treated with 5´-DFUR for gastric cancer for a long time. The patient has been treated with imatinib mesylate 400 mg daily since February 2007. A major cytogenetic response was achieved after 3 months of therapy, as proven by a negative FISH analysis for the bcr-abl transcript. Major molecular response as proven by RT-PCR was achieved after 10 months of treatment. He continues therapy of imatinib, although he has edema and weight gain as adverse effects of imatinib.

Discussion

The development of secondary malignancies is a serious complication after successful chemotherapy and/or radiotherapy for initial malignancy. Most frequently experienced therapy-related malignancies are hematological malignancies, especially acute myeloid leukemia (AML) or MDS (1). On the other hand, acute lymphoid leukemia and CML are rare. Devereux reported only 9 (2.6%) cases of CML in 339 cases of therapy-related leukemia (TRL) (2).

The anti-tumor agents that have been reported to be related to TRL include alkylating agents, topoisomerase-II inhibitors, anti-metabolites, and others. Information about TRL associated with anti-metabolites is sparse (3). Some reports suggest that 5-fluorouracil (5-FU), tegafur, uracil/tegafur (UFT), and other anti-metabolites also might be leukemogenic (4, 5). The types of TRL associated with anti-metabolites are MDS or AML, the as same as alkylating agents or topoisomerase-II inhibitors. At present, the incidence of anti-metabolite-related TRL is unknown, but it is obviously lower than the proportion of leukemias following treatment with alkylating agents or topoisomerase-II inhibitors. Some anti-metabolites are given not only for patients with malignant diseases, but also for non-malignant conditions such as rheumatoid arthritis, psoriasis, sarcoidosis, and myasthenia gravis (6-8). Therefore, the question of whether anti-metabolites may cause TRL is important, especially for patients with non-malignant diseases which tend to require long-term use of drugs.

The present case is the first reported case of CML following 5´-DFUR treatment. 5´-DFUR is an oral fluoropyrimidines. It is not effective itself but it becomes active only after conversion to 5-FU by pirimidine nucleoside phosphorylase, which is preferentially located in tumor tissues (9). Thus, 5´-DFUR produces a higher level of 5-FU in the tumor site than in the normal counterpart (10).

There are 6 case reports of CML following fluoropyrimidines such as 5-FU and S-1. These cases including our case are summarized in Table 1 (11-16). The median age of the 5 man and 2 woman patients was 60 (range 52-74). The primary malignant diseases are all solid tumors such as gastric cancer, colon cancer, esophageal cancer and breast cancer. Four cases received combination chemotherapy. The interval between the diagnosis of the primary disease and CML varied from 12 months to 96 months.

Therapy-related CML is defined as patients with radiotherapy or chemotherapy for malignant disease or non-malignant disease and patients who underwent allogeneic organ transplantation and subsequently received immunosuppressive therapy. Waller et al reviewed 287 published cases of therapy-related CML in 1999 (17), including 221 patients
with malignancies, 28 with nonmalignant disease, and 38 autonomic bomb fallout survivors. Treatment of the 81 patients identified included radiotherapy (n=20), radionuclides (n=14), chemotherapy (n=14), the combination of both (n=19), immunosuppression (n=8) and so on. The median age of the 45 man and 33 woman patients with sufficient information was 42 years (range 2-83). The predominant primary malignancy, including major studies without detailed information, was uterine and cervical cancer (n=44), followed by ovarian cancer (n=37) and Hodgkin’s disease (n=23). Among the nonmalignant conditions, patients receiving immunosuppression after renal transplantation were reported most frequently (n=7). Median interval from initial diagnosis of primary disease to development of CML was 60 months (range 10-252 months). They stated that therapy-related CML cannot be distinguished clinically and cytogenetically from de novo CML. As the molecular or cytogenetic data was not available at the diagnosis of gastric cancer in the present case, we do not know whether the present case already had CML at the diagnosis of gastric cancer. It is an undeniable fact that this case happened to complicate de novo CML. However, the case is suspected to be therapy-related from the fact that 5’-DFUR was administered for long-term of 6 years. The therapy with 5’-DFUR is given about 1 year after curative operation of gastric cancer as standard procedure. It is possible that the long-term 5’-DFUR treatment induced secondary malignancy in this case. If there is no sign of recurrence of initial malignancies, it may be important to avoid inappropriate chronic exposure of anticancer drugs due to the high risk for second malignancies.

Therapy-related AML and MDS have been well characterized. However, therapy-related CML seems to differ from these better-known entities in frequency, clinical course, and prognosis. Although there have not been any major studies providing evidence that therapy-related CML is a frequent late effect of cytotoxic or immunosuppressive therapy, this entity might be increasingly recognized due to a higher number of patients treated with intensive therapy regimens. Large registries appear warranted to assess the real risk of developing therapy-related CML.

References


© 2008 The Japanese Society of Internal Medicine http://www.naika.or.jp/imindex.html