World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v17.i41.4632

World J Gastroenterol 2011 November 7; 17(41): 4632-4634
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

CASE REPORT

S-1 induced secondary acute erythroid leukemia with a chromosome inv(12)(p13;q13)

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Received: January 5, 2011 Revised: March 7, 2011
Accepted: March 14, 2011
Published online: November 7, 2011

Abstract

Adjuvant chemotherapy by S-1 following gastrectomy is considered standard treatment in Japan. Analysis of follow-up data have proved the efficacy of S-1 administration, and that hematological adverse events were relatively rare. Pyrimidine anti-metabolites, including S-1, have shown relatively lower risks for secondary hematological malignancies in comparison to alkylating agents and topoisomerase-Ⅱ inhibitors. We here report a case of therapy-related leukemia after S-1 administration. A patient who had received S-1as the sole adjuvant chemotherapy was diagnosed with acute erythroid leukemia. To the best of our knowledge, our patient represents the first report of S-1 induced acute leukemia.

Key words: S-1; Secondary leukemia; Acute erythroid Leukemia; Gastric cancer

Peer reviewers: Limas Kupcinskas, Professor, Department of Gastroenterology, Kaunas University of Medicine, Mickeviciaus 9, Kaunas LT44307, Lithuania

Matsumoto K, Kitanaka A, Uemura M, Waki F, Fukumoto T, Ohnishi H, Kubota Y, Ishida T. S-1 induced secondary acute erythroid leukemia with a chromosome inv(12)(p13;q13). *World J Gastroenterol* 2011; 17(41): 4632-4634 Available from: URL: http://www.wjgnet.com/1007-9327/full/v17/i41/4632.htm DOI: http://dx.doi.org/10.3748/wjg.v17.i41.4632

INTRODUCTION

S-1 (tegafur + gimeracil + osteracil) oral administration for long periods has been widely used in East Asia as an adjuvant chemotherapy and for a advanced gastric cancer with little caution regarding the development of secondary malignancy[1]. The Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC), a randomized study comparing S-1 adjuvant therapy with surgery only proved the efficacy of S-1adjuvant therapy. In the ACTS-GC study, hematological adverse events of grade 3 or 4 were relatively rare[2].

Therapy-related leukemia (TRL) may be separated into two types. The first type which usually develops 3-6 years after chemotherapy with alkylating agents, is usually preceded by a preleukemic phase. It is associated with specific unbalanced cytogenetic aberrations mostly involving chromosome 5 or 7, with an acute myeloid leukemia (AML) and invariably carries a poor prognosis. The second type is found in patients treated with topoisomerase Ⅱ inhibitors, and lacks a preleukemic phase. Rather, it often develops after a short latency, and presents with

cytogenetic rearrangements specific to *de novo* AML, such as t(8;21), inv(16), t(15;17) or often with a balanced translocation between 11q23 and other chromosomes, primarily t(6;11), t(9;11) and t(11;19)[3-5].

Although alkylating agents and topoisomerase Ⅱ inhibitors are well known as drugs that are related to the development of therapy-related leukemia, pyrimidine antimetabolites, including S-1, have been thought to be rarely associated with the development of leukemia[6]. In fact, therapy related acute leukemia by the sole administration of pyrimidine antimetabolites is very rare. Therapy-related leukemia induced by S-1 has not yet been reported. A recent study, however, revealed that pyrimidine antimetabolites could cause damage to DNA[7].

CASE REPORT

We report a 67-year-old male who developed acute erythroid leukemia after adjuvant chemotherapy using S-1 following distal gastrectomy (D2 resection) for primary gastric cancer (T2N1M0 stage Ⅱ, poorly differentiated adenocarcinoma non-solid type). Peripheral blood analysis showed no abnormalities before chemotherapy.

Ten courses of chemotherapy S-1 (120 mg/d) were orally administered between April 2008 and July 2009. He had not received any other chemotherapeutic agents. In August 2009, peripheral blood analysis demonstrated mild anemia and leukocytopenia. He was referred to our department for further examination. Peripheral blood analysis showed anemia (Hb9.0 g/dL), leukocytopenia (1840/μL) and thrombocytopenia (101 000/mL). Bone marrow aspiration revealed hypercellular marrow with 57.1% of the erythroblasts showing megaloblastic morphologic changes. Blast comprised 38.0% of non-erythroid cells.

Bone marrow pictures revealed morphologically dysplastic nuclei and cytoplasm in all three hematopoietic cell lineages. The patient was diagnosed with acute erythroid leukemia, according to the WHO classification. Immunophenotypical analysis by flowcytometry demonstrated that the leukemic cells were CD 4- CD13+, CD33dim, CD34+, CD56+, CD117+, MPO-/+, TdT- and HLA-DR+. Chromosomal analysis showed 45, XY, del(5q), inv(12)(p13;q13), -17, -17, add (22)(q13), +marl[7]/47, sl, +10, +11, +22, add (22)[4]48, sdl1, +8[2]/46, XY[3].

The patient was initially treated with idarubicin and Ara-C, but failed to achieve complete remission and was subsequently administered an alternative induction chemotherapy regimen [G-CSF + Fludarabine + Ara-C + Mitoxantrone (FLAGM)]. Treatment with salvage chemotherapy failed to induce remission. She died after 3 mo from diagnosis from sepsis and liver failure.

DISCUSSION

The introduction of adjuvant chemotherapy after successful surgical or radiotherapeutic eradication of cancers has been considered to improve relapse-free survival. However, treatment-related malignancy has emerged as a serious complication. The accumulation of genetic aberrations induced by anti-cancer agents in hematopoietic stem cells ultimately leads to myelodysplastic syndrome (MDS)/AML[8]. On the other hand, oral administration of pyrimidine anti-metabolites for long periods has been widely used in Japan as an adjuvant chemotherapy with little caution regarding the development of secondary malignancy.

Abe *et al*[9] reported a case of tegafur-induced AML who developed AML 8 years after starting tegafur (Table 1). This patient showed del(5) chromosomal change, as in our case. Other patients Table 1 were also administrated a large amount of pyrimidine anti-metabolites; in all of them it took at least 24 mo to develop AML. Our patient developed AML after a cumulative S-1 dose of 33.6g only 13 mo after starting S-1.

Acute erythroid leukemia accounts for less than 5% of all leukemia cases. The incidence for leukemia among 65-to-69-year-old males in Japan is $18.9/10^5$ per year[12]. We estimate that the possibility of the coincidence of two malignancies would not be very high given this data. However, the patient's leukocytes might have had an abnormal gene that did not present phenotypically before, and S-1 administration might have caused a further gene mutation that caused the leukemia.

S-1 is a combination preparation consisting of tegafur, gimeracil [5-chloro-2,4-dihydroxypyridine (CDHP)] and oteracil potassium (Oxo) in a molar ratio of 1:0.4:1. CDHP reversibly inhibits the function of dihydropyrimidine dehydrogenase (DPD), which mediates the rate-limiting process of 5-‰Fluorouracil (5-FU) elimination, thereby increasing the plasma concentration of 5-FU. UFT is another combination preparation consisting of tegafur and uracil in a molar ratio of 1:4. Although uracil, like CDHP, inhibits DPD, its inhibitory potency is far weaker than that of CDHP[13]. The content of tegafur in UFT is also 3-to 5-fold higher than that in S-1. Therefore, a short time duration and a small cumulative dose of S-1 could still induce secondary leukemia as in our case. Two cases of S-1 -induced chronic myeloid leukemia (CML) have been reported. The cumulative doses of S-1 were only 41.5 g and 92.5 g, respectively[14]. The present case should serve as a cogent warning that even a relatively short period of S-1 intake may result in the development of lethal leukemia.

Therapy-related leukemias are often refractory to conventional treatment and are associated with poor survival, with a few exceptions such as acute promyelocytic leukemia. As recently reviewed by Pedersen-Bjergaard *et al*[15], survival after post -transplant t-MDS/AML is estimated to be 6 mo.

Manola *et al*[16] reported that t(12;12)(p13;q13) constitutes a disruption of the *ETV6*(*TEL*) gene. The 12p13 region is genetically unstable and fragile, with subsequent translocations and insertions into other chromosomes[17]. It has been reported that multiple chromosome breaks in this region are likely to have been induced through

Table 1 Therapy-related leukemia cases induced by (adjuvant therapy constituted) mainly of pyrimidine anti-metabolites

No.	Age/sex	Primary tumor	Type of treatment for (primary) tumor	Duration from prior therapy (mo)	FAB	Karyotype	Survival duration (mo)	Ref.
1	81/M	Colon	c.r+ 1086 g tegafur/uracil	24	M4	47XY, +8, t(11;17)(q23;q25)	14	[10]
2	54/M	Colon	c.r+ 315 g of UFT +210 mg of MMC	40	M6	44, XY, dic(5;17)(q13;p11), -7, add (15)(q24) 44, as above, -dic(5;17), +mar1	3 >	[11]
3	67/M	Colon rectum	c.r+ 645 g of tegafur, 560 mg of Ara-C, 56 mg of MMC	96	M2	45XY, -5, -6, 7q-, -8, -20, +3mar	6	[9]
4	67/M	Colon	c.r+ 252g of UFT, 80mg of MMC	108	M2	47XY, +1, der(1;7)(q10,p10), -7, +8	10	[9]

c.r: Curative resection; M: Male; UFT: Tegafur/uracil; MMC: Mitomycin C; Ara-C: Cytarabine; FAB: French-American-British classification.

chemo/radiotherapy or mutagens, and are associated with a subgroup of patients with extremely bad prognoses. Although the 12p13 region is considered genetically unstable, t(12;12)(p13;q12~q13) is a rare cytogenetic abnormality. Only one case of therapy-related acute leukemia with t(12;12)(p13;q13) has been reported[16].

Our case suggests that therapy-related leukemia may develop after exposure to pyrimidine anti-metabolites. Thus, S-1 may induce TRL even when used for shorter durations and at lower cumulative doses than other pyrimidine anti-metabolites. Adjuvant chemotherapy by S-1 is a standard therapy for locally advanced gastric cancer in Japan, and is often used in China and Singapore as well. Therefore, more caution should be taken against the possibility of t-MDS/AML caused by S-1 in these countries.

ACKNOWLEDGMENTS

We would like to thank Mr Yamaoka for analyzing surface marker.

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S- Editor Sun H **L- Editor** Kerr C **E- Editor** Xiong L