CASE REPORT

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

Kensuke Matsumoto, Akira Kitanaka, Makiko Uemura, Fusako Waki, Tetsuya Fukumoto, Hiroaki Ohnishi, Yoshitsugu Kubota, Toshihiko Ishida

Kensuke Matsumoto, Akira Kitanaka, Makiko Uemura, Fusako Waki, Tetsuya Fukumoto, Hiroaki Ohnishi, Yoshitsugu Kubota, Toshihiko Ishida, First Department of Internal Medicine, Faculty of Medicine, Kagawa University, 1750-1 Miki-cho, Kita-gun, Kagawa prefecture 761-0793, Japan
Akira Kitanaka, Hematology, Faculty of Medicine, Kagawa University, 1750-1, Miki-cho, Kita-gun, Kagawa prefecture 761-0793, Japan
Yoshitsugu Kubota, Department of Transfusion Medicine, Kagawa University, 1750-1 Miki-cho, Kita-gun, Kagawa prefecture 761-0793, Japan
Author contributions: Matsumoto K, Kitanaka A contributed equally to this work; Uemura M, Waki F, Fukumoto T, Ohnishi H, Kubota Y, Ishida T designed research; Matsumoto K and Kitanaka A wrote the paper.
Correspondence to: Kensuke Matsumoto, MD, PhD, First Department of Internal Medicine, Faculty of Medicine, Kagawa University, 1750-1, Miki-cho, Kita-gun, Kagawa prefecture, Japan. matsumot@med.kagawa-u.ac.jp
Telephone: +81-87-8912145 Fax: +81-87-8912147
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-1 as 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.

S-1 (tegafur + gimeracil + osteracil) oral administration for long periods has been widely used in East Asia as an adjuvant chemotherapy and for 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-1 adjuvant 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

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

Peer reviewers: Limas Kupcinskas, Professor, Department of Gastroenterology, Kaunas University of Medicine, Mickevicius 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 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-1 adjuvant 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)[13-15].

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[9]. 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[17].

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 erythroid blasts 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. Immunophenotypic analysis by flowcytometry demonstrated that the leukemic cells were CD4- CD13+, CD33dim, CD34+, CD56+, CD117+, MPO-/+ , TdT- and HLA-DR+. Chromosomal analysis showed 45, XY, del(5q), inv(12)(p13q13), -17, -17, add (22)(q13), +marl[7]/47, sl, +10, +11, +22, add (22)[4]48, sdel1, +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[10]. 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[10] 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 administered 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 AML cases. The incidence for leukemia among 65-to-69-year-old males in Japan is 18.9/105 per year[13]. 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[14]. 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[16], 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...
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] is a rare cytogenetic abnormality. Only one case of therapy-related acute leukemia with t(12;12) [p13;q13] has been reported (9, 10).

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.

**REFERENCES**

1. **Rosati G**, Ferrara D, Manzione L. New perspectives in the treatment of advanced or metastatic gastric cancer. *World J Gastroenterol* 2009; 15: 2689-2692

2. **Sakuramoto S**, Sasaki M, Yamaguchi T, Kinoshita T, Fuji M, Nishimoto A, Furukawa H, Nakajima T, Ohashi Y, Imamura H, Higashino M, Yamamura Y, Kurita A, Arai K. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med* 2007; 357: 1810-1820

3. **Quesnel B**, Kantarjian H, Bjergaard JP, Brautl P, Estey E, Lai JL, Tilley W, Stoppa AM, Archimbaud E, Harousseau JL. Therapy-related acute myeloid leukemia with t(8;16), inv(16), and (8;16): a report on 25 cases and review of the literature. *J Clin Oncol* 1999; 11: 2370-2379

4. **Pedersen-Bjergaard J**, Sigsgaard TC, Nielsen D, Gjedde SB, Philip P, Hansen M, Larsen SO, Ræth M, Mouridtsen H, Dombrowsky P. Acute monocytic or myelomonocytic leukemia with balanced chromosome translocations to band 11q23 after therapy with 4-epi-doxorubicin and cisplatin or cyclophosphamide for breast cancer. *J Clin Oncol* 1992; 10: 1444-1451

5. **Tasaka T**, Matsuhashi Y, Uehara E, Tamura T, Kakazu N, Abe T, Nagai M. Secondary acute monocytic leukemia with a translocation (8;16) (p11;pl3): case report and review of the literature. *Leuk Lymphoma* 2004; 45: 621-625

6. **Carver JH**, Hatch FT, Branscomb EW. Estimating maximum limits to mutagenic potency from cytotoxic potency. *Nature* 1979; 279: 154-156

7. **Kufe DW**, Herrick D, Gunner L. Uracil enhancement of 5-fluorodeoxyuridine incorporation into human breast carcinoma deoxyribonucleic acid. *Biochem Pharmacol* 1984; 33: 2239-2331

8. **Park DJ**, Koeffler HP. Therapy-related myelodysplastic syndrome. *Semin Hematol* 1996; 33: 256-273

9. **Abe M**, Tanaka Y, Shinohara M, Kosaka M, Matsumoto T. Myelodysplastic syndrome/acute myelogenous leukemia related to adjuvant chemotherapy with oral pyrimidine anti-metabolites. *Br J Haematol* 2000; 111: 712-713

10. **Nakamori Y**, Miyazaki M, Tominaga T, Taguchi A, Shinohara K. Therapy-related erythroleukemia caused by the administration of UFT and mitomycin C in a patient with colon cancer. *Int J Clin Oncol* 2008; 13: 56-59

11. **Fukushima T**, Yoshih N, Noto Y, Kida H. MLL gene rearrangement in acute myelogenous leukemia after exposure to tegafur/uracil. *Int J Hematol* 2002; 75: 178-181

12. **Matsuda T**, Marugame T, Kame K, Katanoda K, Akiwi W, Sobe T. Cancer incidence and incidence rates in Japan in 2005: based on data from 12 population-based cancer registries in the Monitoring of Cancer Incidence in Japan (MCJ) project. *Jpn J Clin Oncol* 2011; 41: 139-147

13. **Errington J**, Mandelstam J. Use of a lacZ gene fusion to determine the dependence pattern and the spore compartment expression of sporulation operon sporVA in spo mutants of Bacillus subtilis. *J Gen Microbiol* 1986; 132: 2977-2985

14. **Uemura Y**, Imai T, Machida T, Shimada K. Secondary chronic myelogenous leukemia following postoperative TS-1 therapy for advanced gastric cancer. *Rinsho Ketsueki* 2010; 51: 559-563

15. **Pedersen-Bjergaard J**, Andersen MK, Christiansen DH. Therapy-related acute myeloid leukemia and myelodysplasia after high-dose chemotherapy and autologous stem cell transplantation. *Blood* 2000; 95: 3273-3279

16. **Manola KN**, Georgakakos VN, Marinakis D, Stavropoulou C, Panos C, Kotsisandos I, Pantelias GE, Sambani C. Disruption of the ETV6 gene as a consequence of a rare translocation (12; 12) (p13; q13) in treatment-induced acute myeloid leukemia after breast cancer. *Cancer Genet Cytogenet* 2005; 180: 37-42

17. **Sato Y**, Kobayashi H, Suto Y, Ohnry HJ, Davis EM, Super HG, Espinosa R, Le Beau MM, Rowley JD. Chromosomal instability in chromosome band 12p13: multiple breaks leading to complex rearrangements including cytogenetically undetectable sub-clones. *Leukemia* 2001; 15: 1193-1202

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

---

**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, del(5)(p13q11), -7, add (15)(q24) | 3 > [11]                     |     |
| 3   | 67/M    | Colon rectum | c-r+ 465 g of tegafur, 560 mg of Ara-C, 56 mg of MMC | 96                              | M2  | 45XY, -5, -6, 7q-, -8, -20, +mar | 6 [9]                                 |     |
| 4   | 67/M    | Colon        | c-r+ 252g of UFT, 80mg of MMC         | 108                             | M2  | 47XY, +1, der(17)(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.