P190$^{BCR-ABL}$ Chronic Myeloid Leukemia Following a Course of S-1 Plus Oxaliplatin Therapy for Advanced Gastric Adenocarcinoma

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Key words: Chronic Myeloid Leukemia; Gastric Cancer; Oxaliplatin; P190$^{BCR-ABL}$; S-1; Therapy-related Leukemia

Secondary malignant neoplasms are important late complications after chemotherapy and/or radiotherapy in cancer patients. Therapy-related malignancies include acute leukemia, myelodysplastic syndrome (MDS), lymphoma, and solid tumors. However, secondary acute lymphoid leukemia or chronic myeloid leukemia (CML) is rarely reported.[1] Here, we present a patient with P190$^{BCR-ABL}$-positive CML following S-1 plus oxaliplatin therapy for gastric adenocarcinoma. The patient has given written informed consent for the use of his medical data.

A 70-year-old male was diagnosed as gastric adenocarcinoma (T2N1M0) in August 2013 and underwent radical gastrectomy in September 2013. Pathology analysis showed adenocarcinoma of the bulge type highly differentiated. The peripheral blood (PB) test before chemotherapy was as following: hemoglobin 143 g/L; white blood count (WBC) 3.78 × 10^9/L; and platelet count 148 × 10^9/L. This patient received adjuvant chemotherapy composed of oral S-1 75 mg twice daily for 14 days plus oxaliplatin 0.2 g once intravenously, without radiotherapy. He demonstrated no evidence of recurrence of gastric cancer.

He was referred to our hospital in May 2015 complaining fever and meteorism. No hepatosplenomegaly was seen. The PB findings were as follows: hemoglobin 79 g/L; WBC 33.5 × 10^9/L with 3% promyelocyte, 15% myelocyte, 19% metamyelocytes, 48% neutrophils, 4% lymphocytes, and 11% monocytes; and platelet count 81 × 10^9/L. The liver and renal functions were in normal range with increased lactate dehydrogenase at 435.4 IU/L (normal range 109.0–245.0). Bone marrow cells were collected and performed the following examinations: (a) cytology showed marked hypercellular marrow with 2.5% myeloblasts, 4.5% promyelocyte, 31.5% myelocyte, 14.5% metamyelocytes, increased number of megakaryocytes, and neutrophil alkaline phosphatase score at 30 (normal range 13–130); (b) cytogenetic analysis revealed 46, XY, t(9;22)(q34; q11.2) in 10 of 10 metaphase cells; (c) molecular analysis by quantitative polymerase chain reaction found P190 positive with negative results for P210 and P230. The diagnosis of CML in the chronic phase was made.

The patient was locally born, worked as a teacher, and did not have relevant family history. He was treated with colchicines for gout for 4 months before the diagnosis of CML. The present case was strongly suspected to be therapy-related leukemia as he was treated with S-1 plus oxaliplatin for gastric cancer. The patient has been treated with imatinib mesylate 300 mg daily from June 2015 and achieved complete hematologic response in 1.5 months. The patient discontinued imatinib due to rash and switched to dasatinib 50 mg daily in September

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Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.199824

Received: 23-08-2016 **Edited by:** Yi Cui
How to cite this article: Wang H, Wang ZY, Xin CH, Shang YH, Jing R, Yan FH, Feng SZ. P190$^{BCR-ABL}$ Chronic Myeloid Leukemia Following a Course of S-1 Plus Oxaliplatin Therapy For Advanced Gastric Adenocarcinoma. Chin Med J 2017;130:495-6.

2015. Cytogenetic response was not assessed because of the patient's personal reason.

In CML, the breakpoints in BCR gene on chromosome 22 (usually between exons e12-e16) and ABL gene on chromosome 9 (in exon a2) result in fusion transcripts encoded for $P210^{BCR-ABL}$. In rare case, fusion transcript involving e1a2 may occur which encodes $P190^{BCR-ABL}$.[2,3] These two transcripts may coexist, but $P190^{BCR-ABL}$ CML only is uncommon representing only 1% of CML. The clinical manifestations and outcome of CML bearing $P190^{BCR-ABL}$ are different from those with $P210^{BCR-ABL}$, demonstrating inferior response to tyrosine kinase inhibitors. $P190^{BCR-ABL}$ CML has been reported to have increased monocytosis and splenomegaly.[4,5] Based on medical history and molecular data, the patient was diagnosed secondary $P190^{BCR-ABL}$ CML and showed monocytosis.

Secondary malignancies are a severe complication after successful chemotherapy and/or radiotherapy for primary malignancy. As a rare complication, secondary CML comprises approximately 2.6% of total secondary leukemia case and secondary $P190^{BCR-ABL}$ CML is far less. Therefore, secondary CML following S-1 treatment is rarely reported. S-1 is an oral fluoropyrimidine, belonging to antimetabolites. In addition to S-1, the patient received oxaliplatin therapy. There was one case report showing secondary acute promyelocytic leukemia following oxaliplatin plus capecitabine therapy[6] while secondary CML following oxaliplatin was not reported yet. As the molecular or cytogenetic data were not available at the diagnosis of gastric adenocarcinoma, we cannot rule out the possibility of existing CML at the diagnosis of gastric adenocarcinoma. However, this case is very likely to be therapy related from the fact that S-1 and oxaliplatin were administrated 2 years before the diagnosis of CML. Compared to the earlier case reports,[7,8] this patient was exposed to shorter duration and fewer doses of S-1.

Reasonable amount of data is available regarding the epidemiology, molecular pathogenesis, clinical manifestations, and treatment response of secondary AML and MDS; however, very little is known about therapy-related CML. Therapy-related CML cannot be distinguished from *de novo* cases both cytogenetically and clinically. Up to now, evidence is lacking as to the frequency of therapy-related CML complicating cytotoxic therapy. It is suggested that complete blood count should be monitored following cancer treatment.

Therapy-related CML is a rare late complication of cytotoxic therapy. It is suggested that complete blood count should be monitored after chemotherapeutic treatment of cancer.

Financial support and sponsorship

This work was supported by the Natural Science Foundation of Shandong Province (No. ZR2013HL001), and the Tianjin Application foundation and advanced technology research program (No. 14JCZDJC33000), China.

Conflicts of interest

There are no conflicts of interest.

References

1. Devereux S. Therapy associated leukaemia. Blood Rev 1991;5:138-45.
2. Quintás-Cardama A, Cortes J. Molecular biology of bcr-abl1-positive chronic myeloid leukemia. Blood 2009;113:1619-30. doi: 10.1182/blood-2008-03-1447 90.
3. Andrikovics H, Nahajevszky S, Szilvási A, Bors A, Adám E, Kozma A, *et al.* First and second line imatinib treatment in chronic myelogenous leukemia patients expressing rare e1a2 or e19a2 BCR-ABL transcripts. Hematol Oncol 2007;25:143-7. doi: 10.1002/hon.822.
4. Verma D, Kantarjian HM, Jones D, Luthra R, Borthakur G, Verstovsek S, *et al.* Chronic myeloid leukemia (CML) with P190 BCR-ABL: Analysis of characteristics, outcomes, and prognostic significance. Blood 2009;114:2232-5. doi: 10.1182/blood-2009-02-204693.
5. Melo JV, Myint H, Galton DA, Goldman JM. P190BCR-ABL chronic myeloid leukaemia: The missing link with chronic myelomonocytic leukaemia? Leukemia 1994;8:208-11.
6. Zhang YC, Zhou YQ, Yan B, Shi J, Xiu LJ, Sun YW, *et al.* Secondary acute promyelocytic leukemia following chemotherapy for gastric cancer: A case report. World J Gastroenterol 2015;21:4402-7. doi: 10.3748/wjg.v21.i14.4402.
7. Higuchi M, Nishinaka H, Yamano Y. A case of chronic myeloid leukemia following TS-1 therapy for advanced gastric cancer. Gan To Kagaku Ryoho 2006;33:2049-52.
8. Uemura Y, Imai T, Machida T, Shima Y. Secondary chronic myelogenous leukemia following postoperative TS-1 therapy for advanced gastric cancer. Rinsho Ketsueki 2010;51:559-63.