



# GASTRIC CANCER AND CML: A LITERATURE REVIEW AND CASE REPORT

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**Abstract** – *Chronic myeloid leukemia (CML) is a hematologic malignancy in which abnormal proliferation of cells in the myeloid series occurs. It is developed by a chromosomal translocation. CML usually develops in adults and rarely in children. The association of chronic myeloid leukemia and gastric cancer is very rare, with only 18 reported cases.*

*Here we report the case of a fifty-year-old Iranian woman who developed CML, then developed a second malignancy (gastric cancer) four years later. She was treated with imatinib (GleevecR), a tyrosine kinase inhibitor.*

*We present the case and review the literature on CML's association with gastric cancer.*

**KEYWORDS:** *Chronic myeloid leukemia (CML), Gastric cancer, Tyrosine kinase inhibitor.*

## INTRODUCTION

Chronic myeloid leukemia (CML) is a stem cell disorder and belongs to the chronic myeloproliferative disease family. Clinically, CML has a chronic phase, an accelerated phase, and a blastic phase. CML can occur without any special signs or symptoms, but patients may exhibit weakness, asthenia, early satiety, or splenomegaly. CML patients have an increased white blood cell count with immature myeloid cells in the peripheral blood. The pathogenesis of CML is due to the Philadelphia chromosome, via chromosomal translocation (9;22). The Philadelphia chromosome is positive in more than 95 percent of cases, and nearly all patients have a positive BCR-ABL translocation.

BCR-ABL activates tyrosine kinase and is detectable in all of the hematopoietic lineage cells. For unknown reasons, the BCR-ABL-induced cellular expansion predominantly targets the myeloid progenitor cell compartment, giving rise to the clinical phenotype<sup>1</sup>. Tyrosine kinase inhibitors (TKIs) are pharmaceutical drugs which inhibit tyrosine kinases. Cell proliferation, differentiation, metabolism, and programmed cell death can be induced by tyrosine kinase<sup>2</sup>. To avoid or minimize these effects, TKIs are the first-line therapy for CML patients with positive BCR-ABL translocation.

The largest family of oncogenes encodes proteins with protein kinase activity. These oncogenes encompass the full variety of protein kinase, including receptor/nonreceptor tyrosine kinases



and cytoplasmic serine/threonine kinases. Many members of this large oncogene group are expressed by the neoplasm of the gastrointestinal (GI) tract, including the receptor tyrosine kinases of the epidermal growth factor receptor (EGFR) family (ERBB1-4) and the nonreceptor tyrosine kinase that associates with the surface of the plasma membrane<sup>3</sup>.

The relationship between protein kinase related oncogenes and GI cancers has been discussed before, but further studies are needed on the relationship of these oncogenes to tyrosine kinase inhibitors. There is a relationship between TKIs and treatment of some gastric malignancies like gastrointestinal stromal tumors (GISTs).

GISTs are rare cancers. However, in 2000 they become targetable by new TKIs, given the role played by KIT gene and platelet-derived growth factor receptor alpha (PDGFRA) in their pathogenesis. In the advanced disease, TKIs have substantially improved the prognosis of KIT-mutated GISTs and have become the standard treatment. GISTs are more complex than initially believed, and though targeted therapy has substantially improved their prognosis it is limited by its apparent inability to eradicate the disease (even minimum residual disease). Research and treatment of advanced GIST were revolutionized by molecularly targeted therapy<sup>4</sup>, such as imatinib therapy. Imatinib (Gleevec<sup>R</sup>) was discovered in 1992<sup>5</sup> and is regarded as a first generation drug since it is the first BCR-ABL TKI to be used in the treatment of CML. Before imatinib approval by the Food and Drug Administration, the most commonly used drugs for the treatment of CML were carcinogens like hydroxyurea, busulfan, or interferon therapy.

In the literature on CML's association with different cancers, CML was seen with colon, rectal, squamous cell, nose, throat and gastric cancer. Researchers previously reported 18 cases of CML associated with gastric cancer (9 cases in Europe and the USA<sup>6-13</sup>, 8 cases in Japan<sup>14-16</sup>, and one case in Turkey<sup>17</sup>). We report a rare case in which CML and gastric cancer presented in a patient who was treated with a TKI.

## CASE PRESENTATION

The patient was a 50-year-old woman with CML and without any familial history of cancer. On May 14, 2008, she was found to have a white blood cell count of 111.1 ( $10^3/\mu\text{l}$ ). The patient was diagnosed with CML on May 17, 2008; her Philadelphia chromosome was reported positive by a nested RT-PCR. Study of her bone marrow showed intensive hyperplasia and increased basophilia, and further-

more most of her myeloid cells were in different stages of development without stopping maturation. Myeloblastic cells were less than 5% (myeloid series). Treatment was started with one 400 mg imatinib (Gleevec<sup>R</sup>) tablet per day. By May 21, 2008, her WBC count became completely normal: 5.5 ( $10^3/\mu\text{l}$ ). According to a cross-sectional study done at Mashhad University of Medical Sciences from 2010 to 2012, there is no relationship between KRAS mutation and CML<sup>18</sup>. So, we did not consider the presence of a KRAS mutation in our case. For four years the patient was in complete hematologic response, until May 17, 2015, when in spite of a normal WBC count (6.5 [ $10^3/\mu\text{l}$ ]) a myeloid blastic phase was suggested due to the presence of blast cells in her peripheral blood smear (PBS).

On May 22, 2015, the patient had an upper gastric endoscopy due to dyspepsia and epigastric pain. The endoscopy revealed a prominent gastric fold and mucosal redness in the body of the stomach. Her esophagus was normal, but a horn-shaped image was seen in her stomach, such that the upper 1/3 of the stomach was dilated and the antro-pyloric canal was significantly narrowed. Infiltrative carcinoma in inferior 1/3 of the stomach was approved. Gastric mucosa was taken for a biopsy. The biopsy result showed a suspected positive result for diffuse types of adenocarcinoma (by the H & E method). Surgery was recommended, but the advanced stage of the adenocarcinoma made it inoperable. After that inoperable surgery, the patient stopped the whole therapy and she died after 3 months.

## DISCUSSION

As mentioned above, eighteen cases of CML associated with gastric cancer have been reported<sup>6-17</sup>. Moertel and Hagedorn reported that leukemia increased the cancer incidence rate<sup>17, 19</sup>. Stomach, breast, and esophageal cancers were commonly seen (in 8.3% out of 674 patients) in patients with a hematological malignancy, as reported by Niitsu and Umeda<sup>17,20</sup>. Carruth and colleagues reported on an 18-year-old male CML patient with a positive Philadelphia chromosome associated with adenocarcinoma<sup>8,17</sup>. The 16<sup>th</sup> case of CML association with gastric cancer was a 59-year-old white female from the USA that had started treatment with busulfan in March 1981 and continued until February 1983. At that time the therapy was changed to hydroxyurea. Invasive aspergillosis caused her death in November 1984<sup>6</sup>.

The last case reported was a 47-year-old male patient in Turkey. The patient's BCR-ABL fusion gene was found to be positive, and treatment with

hydroxyurea 2 g/day and interferon therapy  $\alpha$  2b were started. Development of thrombocytopenia during the interferon therapy compelled doctors to stop this treatment, and replace it with imatinib (mesylate) 400 mg/day. The patient used imatinib (mesylate) for three years<sup>17</sup>. Despite a widespread search, we were unable to find further information about this case.

Except for this last case, all the previous studies reported carcinogenic treatments such as hydroxyurea and busulfan and interferon therapy. As noted, the Turkish patient started with hydroxyurea and interferon but switched to imatinib later. Our case is the 19<sup>th</sup> case linking CML to gastric cancer. Our Iranian patient used imatinib for four years, but didn't use busulfan, hydroxyurea, interferon therapy, or any other carcinogenic drug. After four years, her second malignancy occurred, diffuse infiltrative gastric cancer (limit ballistic).

## CONCLUSIONS

The association between TKIs and secondary malignancy has not been previously reported, but given our results it may have been a contributing factor to the patient's gastric cancer. Given these results, and the previous studies on CML and other cancers, we recommend that doctors pay close attention to potential signs of gastric cancer in CML patients.

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## CONFLICT OF INTERESTS:

The Authors declare that they have no conflict of interests.

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