## Development of c-Kit-expressing Small-Cell Lung Cancer in a Chronic Myeloid Leukemia Patient During Imatinib Treatment

Imatinib inhibits the activities of three oncogenic tyrosine kinases—Abl, c-Kit, and platelet-derived growth factor receptor (PDGFR)—with similar affinity. Imatinib exerts important clinical activities in cancers in which any of these three tyrosine kinases play a causal role in the transformation process (e.g., Abl and chronic myeloid leukemia [CML]) *(1–3).* In particular, imatinib has marked clinical activity in patients affected by gastrointestinal stromal tumors (GIST), a type of cancer frequently caused by activating mutations of c-KIT; in this setting, the presence of c-KIT mutations are an important predictor of the clinical response to imatinib *(4).*

Although c-Kit and PDGFR are expressed in several more common cancers, such as prostate cancer and glioblastomas (PDGFR) or small-cell lung cancer (SCLC; c-Kit), the absence of a structural alteration such as a mutation makes their relationship to malignant transformation less evident than that of c-Kit to GIST and thus the rationale for imatinib use in these cancers is weaker than it is for CML and GIST. Nonetheless, the use of imatinib to treat SCLC is particularly intriguing because this cancer has been found to express stem cell factor, the ligand of c-Kit *(5).* However, no mutations in the c-KIT gene or structural alterations in the c-Kit protein have been reproducibly found in SCLC. Here we report on an exceptional case that illustrates the difference between the two categories of tumors: those with structurally altered tyrosine kinases and those that just express them. A 50-year-old male patient (FP) with interferon-resistant chronic-phase CML was started, after providing written informed consent, on imatinib (400 mg/day) in December of 1999. He tolerated the treatment without any major side effect and had a complete cytogenetic response by June of 2000. The dosage of imatinib was increased to 600 mg/day in October of 2001, and the patient subsequently (since May of 2002) tested negative for the Bcr-Abl transcript by a nested reverse transcription–polymerase chain reaction assay (>3 logs decrease by quantitative PCR).

The patient continued to smoke 20–30 cigarettes per day while receiving imatinib treatment. In May of 2003, he complained of shortness of breath and asthenia. A left pleural effusion was present, and a mediastinal mass of 9 cm originating from the left main bronchus was identified by chest x-ray and CAT scan. The patient underwent bronchoscopy and was subsequently diagnosed with SCLC. No evidence of metastatic disease was found.

Figure 1 shows that cells obtained from the original lung tumor biopsy sample from this patient showed uniform cytoplasmic expression of c-Kit protein when stained with an anti-Kit antibody. Sequencing of exons 9, 11, and 13 of the c-KIT gene in DNA isolated from the tumor biopsy sample revealed no mutations or deletions.

Because the lung tumor was not amenable to radical surgery, the patient was treated with three cycles of cyclophosphamide–epirubicin–vincristin, followed by three cycles of carboplatin–etoposide. He obtained a very good partial response (87% reduction in tumor area) and underwent consolidation x-ray treatment (5500 cGy). To avoid possible interference between imatinib and the cytotoxic drugs *(6)*, imatinib treatment was temporarily discontinued in June of 2003 and resumed after the completion of chemotherapy in November of 2003. Unfortunately, the patient developed a central nervous system relapse in January of 2004 and, despite further x-ray treatment, died of progressive SCLC in May of 2004, while his CML was still in cytogenetic and molecular remission.

A preliminary report has documented the low antitumor activity of imatinib in patients affected with advanced SCLC *(7).* However, in the patient reported on

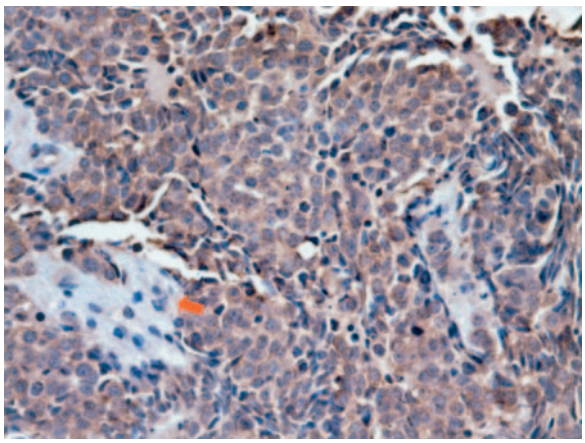

**Fig. 1.** Expression of c-Kit protein in small-cell lung cancer cells obtained from the diagnostic biopsy sample of patient FP detected after autoclave antigen retrieval by immunohistochemistry with a rabbit polyclonal anti-human CD117 (c-Kit) antibody (A4502, 1:50 dilution; Dako, Glostrup, Denmark). Neoplastic cells displayed uniform cytoplasmic staining for c-Kit expression (**brown**), whereas stromal cells did not (**arrow**). Magnification ×914.

here, the tumor actually developed while the patient was being treated with imatinib and despite the uniform expression of c-Kit in his tumor. This case epitomizes the importance of targeting early events in cancer that are causally related to the transformation process.

CARLO GAMBACORTI-PASSERINI
ROCCO PIAZZA
LUCIA TORNAGHI
SILVANA PILOTTI
ENRICO POGLIANI

## REFERENCES

*(1)* Druker BJ, Tamura S, Buchdunger E, Ohno S, Segal GM, Fanning S, et al. Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells. Nat Med 1996;2:561–6.

*(2)* Kantarjian H, Sawyers C, Hochhaus A, Guilhot F, Schiffer C, Gambacorti-Passerini C, et al. Hematologic and cytogenetic responses to imatinib mesylate in chronic mylogenous leukemia. New Engl J Med 2002;346:645–52.

*(3)* Gambacorti-Passerini C, Gunby R, Piazza R, Galietta A, Rostagno R, Scapozza L. Molecular mechanisms of resistance to imatinib in Ph-positive leukemias. Lancet Oncol 2003;4:75–85.

*(4)* Heinrich MC, Corless CL, Demetri GD, Blanke CD, von Mehren M, Joensuu H, et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. J Clin Oncol 2003;21:4342–9.

*(5)* Krystal GW, Hines SJ, Organ CP. Autocrine growth of small cell lung cancer mediated by coexpression of c-kit and stem cell factor. Cancer Res 1996;56:370–6.

*(6)* Ruchatz H, Puttini M, Cleris L, Formelli F, Pilotti S, Gambacorti-Passerini C. Effect of STI571 on haematopoietic recovery following idarubicin exposure. Leukemia 2003;17:298–304.

*(7)* Johnson BE, Fischer T, Fischer B, Dunlop D, Rischin D, Silberman S, et al. Phase II study of imatinib in patients with small cell lung cancer. Clin Can Res 2003;9:5880–7.

## NOTES

*Affiliations of authors:* University of Milano Bicocca/National Cancer Institute, Milan, Italy, and McGill University, Montreal, Canada (CG); University of Milano Bicocca, Milan, Italy (RP); National Cancer Institute Milano and San Gerardo Hospital, Monza (LT); National Cancer Institute, Milan (SP); University of Milano Bicocca and San Gerardo Hospital, Monza, Italy (EP).

*Correspondence to:* Carlo Gambacorti-Passerini, MD, University of Milano Bicocca C/O National Cancer Institute, Via Venezian 1, 20133 Milano, Italy (e-mail: carlo.gambacorti@Istitutotumori.mi.it).

MIUR-COFIN and PRINprograms (2002, 2003) to C. Gambacorti-Passerini.

DOI: 10.1093/jnci/djh330