

## Editorial

# Imatinib for Small Cell Lung Cancer, Aiming for a Target *in Vivo*

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There are an estimated 25,000 patients who develop small cell lung cancer per year in the United States. The currently available therapy is inadequate because >95% of patients die from their small cell lung cancer (1, 2). The work with conventional chemotherapy has not dramatically altered the relatively poor outcome for patients with small cell lung cancer in the past 20 years (1, 2). There is an ongoing effort to identify effective therapeutic agents developed against molecular targets in patients with lung cancer. Perhaps equally as important is the ongoing effort to determine why drugs aimed at a specific target do not have the anticipated efficacy.

This article provides important *in vivo* information about attempting to use imatinib as a therapeutic agent for patients with small cell lung cancer. The data presented in the article add important information to the recently reported clinical trial of imatinib for patients with small cell lung cancer (3). The clinical trial of 19 patients with small cell lung cancer showed that only 4 of the 19 patients studied had immunohistochemical evidence of the c-kit receptor, and there were no objective tumor responses in any of these patients. The study of the patients with small cell lung cancer documented that the mean maximal plasma concentration of imatinib reached 7.4  $\mu\text{M}$  but did not assess drug levels in the tumors, phosphorylation status of the c-kit receptor in the tumors, or study the tumors for the presence of mutations in *KIT* gene coding for the receptor. Therefore, information has not been available to determine whether the drug did not have evidence of clinical activity because the tumor was not sensitive to the drug, whether adequate amounts of drug reached the tumor, or whether the drug was able to inhibit the signaling through the c-kit receptor as assessed by the phosphorylation status of the receptor.

Wolff *et al.* (4) provide important *in vitro* and *in vivo* data that add to our knowledge about attempts to therapeutically exploit the c-kit receptor in small cell lung cancer. They studied small cell lung cancer cell lines in common use that have been extensively characterized. The cell lines NCI-H209, H526, and H1607 have *in vitro* evidence of functional c-kit receptors because the receptors are phosphorylated. They show that the c-kit receptors increase their phosphorylation status upon stimulation with the agonist, stem cell factor, and that stimulation in some of the cell lines can be inhibited by concentrations of imatinib as low as 0.1  $\mu\text{M}$ , but concentrations of 1–3  $\mu\text{M}$  are

required to completely block the phosphorylation of the c-kit receptor after stimulation with its agonist, stem cell factor, concentrations that can be achieved in human plasma (3).

The cell lines NCI-H209, H526, and H1607 were studied *in vivo*. The investigators show that peak concentrations of imatinib were an average of 3.8  $\mu\text{M}$  in the tumor but declined to 0.6  $\mu\text{M}$  8 h after the oral dose, a concentration where imatinib does not have its maximal effect on the phosphorylation status of the receptor in the *in vitro* studies. There was no significant inhibition of growth in the murine model. Therefore, the treatment of small cell lung cancer with imatinib in humans and in murine models does not yet show any evidence of efficacy despite achieving plasma concentrations that are associated with inhibition of growth of small cell lung cancer *in vitro*.

Oral imatinib mesylate therapy is effective therapy for patients with one of the solid tumors, gastrointestinal stromal tumors. Wolff *et al.* (4) point out that c-kit is overexpressed and constitutively activated by mutations in the gastrointestinal stromal tumors. Additional work has shown that 88% of 112 gastrointestinal tumors have activating mutations of the *KIT* gene (5). The *in vitro* growth of gastrointestinal stromal tumor cells with *KIT* mutations is inhibited by concentrations as low as 0.1  $\mu\text{M}$  of imatinib (5, 6). Furthermore, patients whose gastrointestinal stromal tumors have *KIT* mutations are more likely to respond to treatment with imatinib and live longer than patients without mutations. Therefore, the activating mutations of *KIT* play an important role in the sensitivity and efficacy of imatinib in both *in vitro* and in clinical studies.

The preclinical information has shown that stem cell factor is produced by small cell lung cancer, c-kit receptors were present on the surface of the small cell lung cancer cells, and the phosphorylation can be blocked *in vitro* by incubating the cells with imatinib. The new information presented by Wolff *et al.* (4) shows the *in vivo* growth of small cell lung cancer is not inhibited by the oral administration of imatinib. There are a number of potential explanations for these findings. Perhaps the most important is that 68 small cell lung cancer cell lines and tumors studied thus far do not have activating mutations in the *KIT* gene and are therefore not very sensitive to imatinib (7, 8). The concentrations that inhibit the *in vitro* growth of small cell lung cancer cells are approximately 10–50-fold higher than the concentrations that inhibit the *in vitro* growth of gastrointestinal stromal tumors (5, 6, 9, 10). Therefore, the concentrations achieved by oral administration in mice and humans may not be adequate to inhibit the growth of small cell lung cancer. The authors show that the concentrations of imatinib reach 0.6  $\mu\text{M}$  8 h after dosing and may not be consistently high enough to cause growth inhibition of the small cell lung cancer in the mice.

The use of molecularly targeted agents directed against solid tumors with mutations in the appropriate receptor have been clinically successful in gastrointestinal stromal tumors. A more widely applicable therapeutic use is when the receptor is present and active but has not undergone an activating mutation. The initial clinical data has shown that there is no obvious

Received 2/13/04; accepted 2/24/04.

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evidence of antitumor activity in a small Phase II trial with imatinib for patients with small cell lung cancer. The studies by Wolff *et al.* (4) have provided supporting evidence that there is no evidence of antitumor activity in a murine model. This provides additional evidence that further testing with *in vivo* studies of targeted agents directed against receptors without activating mutations may be helpful in developing the rationale before embarking on an expensive, time consuming, and potentially ineffective clinical trials.

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