Taking Aim at Ewing’s Sarcoma: Is KIT a Target and Will Imatinib Work?

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Ewing’s sarcoma is the second most common primary bone tumor in children. Although the cure rate for localized disease is approximately 50%, it requires intensive multiagent chemotherapy, surgery, and radiation therapy. Patients with metastatic, recurrent, or refractory disease have a much poorer prognosis. In this issue of the Journal, Merchant et al. (1) evaluate the sensitivity of Ewing’s sarcoma cell lines to imatinib. Ewing’s sarcoma cells express the KIT tyrosine kinase and stem cell factor, the ligand for this receptor, thereby closing an autocrine growth stimulatory loop (2,3). Given that KIT is inhibited by imatinib (4,5), it is logical to determine whether this drug inhibits the growth of these cells. Although Merchant et al. (1) show that imatinib does inhibit the growth of Ewing’s sarcoma cells in vitro and in vivo, their report raises two crucial questions. One is whether KIT is the target of imatinib in these cells, and the second is whether imatinib will be a useful therapeutic agent for patients with Ewing’s sarcoma.

The first task is to reconcile their results with another report (6) that concludes that Ewing’s sarcoma cell lines are insensitive to imatinib. In an article by Hotfilder et al. (6), the growth of eight Ewing’s sarcoma cell lines, including two of the same lines used by Merchant et al., was marginally inhibited by imatinib at doses less than 10 μM (6). However, some growth inhibition of Ewing’s sarcoma cell lines was observed with 10 μM imatinib, with greater inhibition at much higher doses (6). Merchant et al. (1) show that the concentration of imatinib required to inhibit 50% of the growth (IC50) of Ewing’s sarcoma cell lines was 10–12 μM. Thus, both agree that imatinib does inhibit the growth of Ewing’s sarcoma cell lines, but at doses greater than 10 μM.

The growth of chronic myelogenous leukemia (CML) cell lines that express the BCR-ABL tyrosine kinase and gastrointestinal stromal tumor cell lines that express KIT kinase-activating mutations is inhibited by concentrations of imatinib that closely match those that inhibit these respective enzymes (7–10). In contrast, the IC50 value for cellular proliferation of Ewing’s sarcoma cell lines is 10–50 times higher than the IC50 for KIT kinase activity in the same cells (1). These data quite strongly imply that KIT is not the primary target for imatinib in Ewing’s sarcoma cells and lead to the inescapable conclusion that expression of KIT does not equate with a critical role for KIT in the growth and survival of Ewing’s sarcoma cells.

The lesson that expression does not necessarily equate with pathogenesis was most evident in a clinical trial of imatinib in gastrointestinal stromal tumors (11). In this study (12), the mutational status of KIT was associated with response to imatinib and survival. Specifically, patients whose tumors express one of the most common KIT-activating mutations have a response rate of 72% and overall survival of 95% with a median follow up of 15 months. In contrast, patients whose tumors express wild-type KIT with no mutations have only an 11.8% response rate with a median survival of 8.3 months. Thus, in patients whose tumors express wild-type KIT, it appears that KIT is not essential for the growth and survival of these tumors. Rather, some indication of aberrant activity of KIT is necessary for it to be a good target in gastrointestinal stromal tumor patients. Although these data suggest that KIT is not a particularly attractive target in Ewing’s sarcoma, it is possible that inhibition of KIT would lead to increased sensitivity of these cells to growth inhibition. In this scenario, KIT tyrosine kinase activity may not be essential for the growth and survival of Ewing’s cells, but inhibition of its kinase activity might make these cells more susceptible to targeting of another pathway.

So, if KIT is not the target for imatinib in Ewing’s sarcoma cell lines, then what is? Imatinib has been tested for its inhibitory activity against 40–50 different tyrosine kinases. Of these, the only kinases inhibited by imatinib at the submicromolar level are KIT, c-ABL and its oncogenic versions (BCR-ABL and v-ABL), the ABL-related gene (ARG), and the platelet-derived growth factor receptors (PDGF-R) α and β (7,13). If any of these kinases were the target for imatinib in Ewing’s sarcoma cells, then their growth should be inhibited at much lower doses of imatinib. Because there are 90 tyrosine kinases in the human genome (14), it is possible and even likely that all of the targets for imatinib have not been determined.

An example of a disorder where the imatinib-sensitive kinase has not been identified is hypereosinophilic syndrome. This disease is highly responsive to extremely low doses of imatinib (15), doses that resulted in minimal responses in the phase I clinical trials of imatinib in CML (16). Because PDGF-R, c-KIT, and the ABL kinases have similar IC50 values for imatinib, it is likely that hypereosinophilic syndrome is driven by an unidentified target of imatinib, or partial inhibition of one of the known kinases may be responsible for the remarkable activity of imatinib in this disorder.

In surveying potential imatinib-sensitive kinases in Ewing’s sarcoma, it is worth noting that imatinib loses some specificity at doses greater than 10 μM. For example, LCK has an IC50 value in the 10 μM range, whereas other kinases, such as the epidermal growth factor receptor, have IC50 values well over 100 μM (8). Importantly, if the kinase inhibited by imatinib in Ewing’s sarcoma were identified, it might unveil a potentially useful target. If the target turns out to be a kinase that is only partially inhibited by imatinib yet results in growth inhibition of these tumor
cells, it is possible that a more potent inhibitor could be an extremely useful therapeutic agent.

The final question is whether imatinib will be an effective therapeutic agent for patients with Ewing’s sarcoma. The maximally tolerated dose of imatinib in phase I clinical trials was close to 1000 mg/day (16–18). At this dose, the blood levels of imatinib were in the range of 6–10 μM (19). This concentration is at or below the IC$_{50}$ value required to inhibit the growth of Ewing’s sarcoma cells, and it is likely that doses closer to the IC$_{50}$ value would be necessary for maximal antitumor effect. Thus, on the basis of this preclinical work, imatinib would, at best, be expected to slow the growth of Ewing’s sarcoma cells. The possibility of using imatinib to increase the sensitivity of Ewing’s sarcoma to other agents could be addressed in future experiments. However, the promise of the findings by Merchant et al. is that there is a kinase in Ewing’s sarcoma cells that, if identified, could lead to improved therapy for this disease.

REFERENCES


NOTE

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