

## Comment



## Imatinib treatment of metastatic GIST: don't stop (believing)

The use of imatinib to treat chronic myeloid leukaemia (CML) and gastrointestinal stromal tumours (GIST) represents the first successful application of small molecule tyrosine-kinase inhibitors (TKIs) to treat human cancer. Imatinib targets genomically activated kinases in these diseases; *BCR-ABL1* in the case of CML and *KIT* (or *PDGFRA*) in the case of GIST. These results validated the principle of identifying and selectively targeting genomically activated oncogenes in human cancers, particularly those that are so-called oncogene addicted. The revolution brought by imatinib in treating CML and GIST led to the testing and approval of additional TKIs to treat these diseases. Ongoing clinical and experimental studies of these diseases continue to yield insights relevant to the treatment of other human cancers.

Over the past decade, parallel insights into the optimum clinical management and underlying biology of CML and GIST have been made. In *The Lancet Oncology* today, Le Cesne and colleagues<sup>1</sup> report the results of a randomised study of GIST patients who had maintained control of their metastatic disease with 3 years of imatinib treatment. Patients were then randomly assigned to continue or interrupt imatinib treatment. The median time to progression was 9 months after assignment to the interruption group and was not reached in the continuation group ( $p < 0.0001$ ). After a median follow-up of 35 months after random assignment, 2-year progression-free survival was 80% in the continuation group versus 16% in the interruption group ( $p < 0.0001$ ). Fortunately, re-introduction of imatinib upon tumour progression in patients in the interruption group was associated with 100% tumour control (no further progression). These results were similar to those reported by the same investigators for identical cohorts of imatinib-responding patients after 1 year of imatinib treatment.<sup>2</sup> Strikingly similar findings have been made in studies of imatinib discontinuation in responding CML patients.<sup>3</sup>

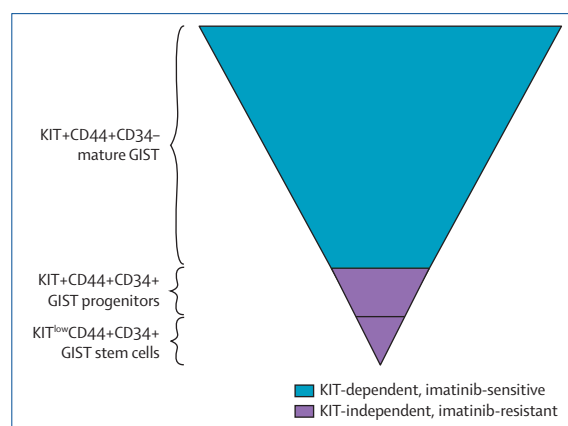
Mathematical and experimental modelling of CML shows that the stem-cell population is not dependent upon *BCR-ABL1*. Accordingly, pharmacological inhibition of *BCR-ABL1* is insufficient to induce

apoptosis and eradication of the mutant-stem-cell population.<sup>4,5</sup> Recently, parallel findings have been noted in the case of GIST.

Bardsley and colleagues<sup>6</sup> have identified  $KIT^{low}CD44+CD34+$  cells isolated from the stomach as clonogenic cells capable of self renewal and differentiation into interstitial cells of Cajal (ICC). Notably, ICC represent the suspected cell of origin for GIST. Proliferation of cultured  $KIT^{low}CD44+CD34+$  ICC precursors was unaffected by treatment with neutralising monoclonal antibodies to *KIT* or by imatinib treatment. Additionally, numbers of ICC stem cell were not reduced in mice with germline inactivation of *KIT* (compared with wild-type mice). However, the number of mature, fully differentiated, ICCs was substantially decreased in mice with germline inactivation of *KIT*.<sup>6</sup>

Bardsley and colleagues also measured populations of ICC stem cells and progenitor cells in a mouse model of GIST induced by a germline activating *KIT* mutation. This particular mutation, homologous to that seen in some GIST kindreds, led to a two-times increase in ICC stem cells compared with control mice lacking the activating mutation. In-vivo imatinib treatment substantially reduced the numbers of  $KIT+CD44+CD34-$  ICC, but did not reduce  $KIT^{low}CD44+CD34+$  ICC stem cells

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**Figure: Proliferation and survival of GIST stem and progenitor cells is KIT-independent and is unaffected by imatinib treatment**

By contrast, the proliferation and survival of mature GIST cells is KIT-dependent and these cells are sensitive to imatinib treatment (blue). Clinical treatment with imatinib debulks GISTs of differentiated cells but does not eradicate GIST progenitor or stem cells (purple). Continuous imatinib treatment is needed to prevent repopulation of GIST tumours from the underlying resistant progenitor-cell or stem-cell pool.

or KIT+CD44+CD34+ immature ICC (figure). By contrast, salinomycin (a selective inhibitor of breast cancer stem cells), completely inhibited the growth of the ICC stem cells. Submaximum doses of salinomycin combined with imatinib caused a substantially greater inhibition of cell proliferation than salinomycin alone.<sup>6</sup>

Taken together, these clinical and experimental findings support the need for continuous treatment with TKIs in CML and GIST, and by extension in other cancers responsive to such drugs. Interruption of treatment is associated with a fairly rapid repopulation of differentiated cancer cells from an underlying intact population of stem and progenitor cells. These findings also suggest that current efforts to improve the potency of TKIs against the activated oncogenes in CML and GIST (including common forms of secondary resistance mutations) might improve the duration of disease control, but will not be sufficient to achieve a cure. Therapies that can eradicate the initiating stem cells are needed for the cure that eludes current treatment with TKIs.

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