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EDITORIAL

Clone wars in CML

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In many recent leukemia presentations, the suggestion that leukemia can be turned into a long-term minimum residual disease, consistent with prolonged life, but without offering the prospect of cure, is raised. Obviously, any intervention that prolongs life at a reasonable quality of life is a significant advance. However, there is precious little evidence to support the notion that leukemia can lie dormant for many years without undergoing genetic change. Such changes are usually associated with eventual clinically overt relapse and resistance to subsequent therapy. Imatinib has transformed the survival potential for patients with chronic phase CML, has had a significant impact for those in accelerated phase and had a minimal impact for those patients with blastic phase disease.[1] It is clear that most patients in chronic phase who have clinically responded to imatinib and who have achieved complete cytogenetic responses have easily detectable disease at the molecular level. The connection between the amount of 'residual' disease, detectable abl mutations in the leukemic cells and overt evidence of relapse at the molecular, cytogenetic or hematological levels is a major focus of interest at present.[2] The qualitative and quantitative relationships between non-mutated and mutant clones are not well understood. The percentage of patients with detectable mutations varies markedly by report and by stage of disease. The mechanism of resistance in approximately half of the patients who have acquired imatinib resistance but no detectable mutation is unclear. A major emerging issue is that of patient compliance and persistence – patients are not good at taking oral medications long-term. Possible mechanisms of true imatinib resistance that do not involve abl mutations include over-expression of Bcr-abl, increased MDR activity, cytogenetic progression or possibly the involvement of other kinases including members of the src family.[1] The next generation abl-kinase inhibitors AMN-107 and Dasatinib can both inhibit *in vitro* all of the common Bcr-abl mutations except T315I.[3–5] In patients, the activity of either drug against most of these mutations, except T315I, has been seen (Giles F *et al*. A phase I/II study of AMN107, a novel aminopyrimidine inhibitor of Bcr-Abl, on a continuous daily dosing schedule in adult patients with imatinib-resistant advanced phase chronic myeloid leukemia or relapsed/refractory Philadelphia chromosome acute lymphocytic leukemia. *ASH Annual Meeting Abstracts* 2004; **104**: 22; Hochhaus A *et al*. Efficacy of Dasatinib in patients with chronic phase Philadelphia chromosome-positive CML resistant or intoleant to imatinib: first results of the CA180013 'START-C' phase II study. ASH *Annual Meeting Abstracts* 2005; **106**: 41).

Khorashad *et al*.[6] in their article on this issue have significantly advanced our understanding of this complex problem. Using pyrosequencing to quantitate non-mutated and mutated alleles in patients with acquired resistance to imatinib, they describe three contrasting kinetic patterns. In one group of patients in whom the mutant allele predominates, with high transcript numbers, we can reasonably assume that the abl mutation is the predominant cause of imatinib resistance. In a second group of patients in whom the mutant allele predominates, but the overall transcript level is low, it appears that the allele may indeed mediate some resistance, but imatinib is still able to suppress most of the disease. In a third group, despite a constant low level of mutant allele, the total levels of transcripts fluctuated, indicating that the overall imatinib sensitivity of the leukemia was variable. Thus, these data indicate that the presence of a mutant abl clone is not enough to account for resistance to imatinib in all patients and that a mutation does not necessarily confer a proliferate advantage over non-mutated clones. These observations have at least two critical implications, the first of which is that we must continue to attempt to eradicate disease as quickly as possible. In CML, current data would indicate that the earlier one achieves a major molecular emission in chronic phase, the more likely one is to retain it. As molecular remission is associated with a minimal chance of relapse, this should probably now become the accepted therapeutic goal for patients with chronic phase CML. The second inference is that there are certainly some patients to whom we have little chance of offering elimination of all malignant clones if we rely purely on one approach, including relying on Bcr-abl inhibitors. If abl mutations are not enough to explain resistance, then it is clearly likely that other mechanisms, including non-Bcr-abl-dependent disease accelerants, are the issue. These mechanisms cannot be expected to respond to further more powerful abl kinase inhibitors – the duration of response to AMN107 or Dasatinib in patients with imatinib-resistance blastic phase disease is brief in most patients (Giles F *et al*. A phase I/II study of AMN107, a novel aminopyrimidine inhibitor of Bcr-Abl, on a continuous daily dosing schedule in adult patients with imatinib-resistant advanced phase chronic myeloid leukemia or relapsed/refractory Philadelphia chromosome acute lymphocytic leukemia. *ASH Annual Meeting Abstracts* 2004; **104**: 22; Sawyers CL *et al*. Dasatinib (BMS-354825) in patients with chronic myeloid leukemia and Philadelphia-chromosome positive acute lymphoblastic leukemia who are resistant or intolerant to imatinib: update of a phase I study. *ASH Annual Meeting Abstracts* 2005; **106**: 38). We have an embarrassment of riches in terms of potential second or third drugs that may be necessary; other inhibitors that may be of relevance include those that target vascular endothelial growth factor, Mtor and aurora kinase.[6,7] HSP90 inhibitors may be able to enhance destruction of an oncoprotein regardless of its mutational status, and because of the number of client proteins that HSP90 chaperones, by exposing a number of client proteins to destruction simultaneously we may affect multiple pathways in a synergistic manner. Whatever the precise methodologies, the notion that we can 'negotiate' long term with CML is probably false and emphasis should remain on early disease elimination as the best chance of offering cure. To what extent we need to adapt our approach to cope with 'quiescent' cells will be a critical issue.[8,9]

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