leading to exchange of corepressor proteins for coactivator complexes and activation of gene transcription.[2] The data presented by Fazi et al indicate that AML1/ETO may interfere directly with RARα function by binding to the receptor in a ligand-independent manner, thus also blocking the ability of ATRA to mediate coregulator exchange and preventing activation of RARα target gene expression. It remains to be seen whether AML1/ETO interacts with other nuclear receptors, but given its positive role in stem/progenitor cell self-renewal, it is interesting to speculate that AML1/ETO may also act upon a closely related RAR family member, RARγ, which has been shown to be critical for maintaining a balance between hematopoietic stem cell self-renewal and differentiation.[3]

So, what is the relevance of these findings for AML therapy? This study further underlines the importance of developing optimized combinatorial therapies that target multiple facets of the biologic activities of a given oncoprotein. In the case of AML1/ETO-associated AML, this study provides a rationale for the use of drugs such as eriocalyxin B and oridonin,[4] which specifically degrade AML1/ETO, combined with differentiation therapy (ATRA and myelomonocytic growth factors). Drugs that reverse epigenetic modifications that negatively regulate gene expression, such as histone deacetylase and DNA methylation inhibitors, have been used in combination with ATRA to treat relapsed and therapy-resistant AML with encouraging results.[5] This study highlights the possibility that t(8;21)-positive AML patients may represent a particularly suitable target population for this type of epigenetic/differentiation therapy and further investigation in this area is warranted.

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CLINICAL TRIALS AND OBSERVATIONS

Comment on Guilhot et al, page 4143

Dasatinib in accelerated phase

Stephen O'Brien NEWCASTLE UNIVERSITY

The paper by Guilhot and colleagues extends the reported clinical experience with dasatinib in describing the outcome of 107 chronic myeloid leukemia (CML) patients treated with the drug in accelerated phase having failed, or been intolerant of, imatinib. Although the follow-up is quite short (8 months minimum), the results are encouraging even in this difficult phase of the disease.

The long-term durability of responses to imatinib in patients with early chronic-phase CML has recently been reported,[1] and thankfully the occurrence of drug resistance in this group of patients remains low. In chronic-phase patients who do develop imatinib resistance or intolerance, dasatinib has been shown to be effective salvage therapy,[2] producing complete hematologic response (CHR) and major cytogenetic response (MCR) rates of 90% and 52%, respectively.[3] Dasatinib has also been shown to be superior to higher-dose imatinib (800 mg) in rescuing patients failing on imatinib 400 mg.[4]

The data presented in this issue describe CHR and MCR rates in accelerated phase of 39% and 33%, respectively, with 24% managing to achieve a complete cytogenetic response (CCR)—quite an achievement in this difficult group of patients. The follow-up is short and so far of 69 patients who achieved good hematologic responses, 7 have progressed. The durability of the responses is, of course, still uncertain until longer follow-up is reported. The Achilles heel of both dasatinib and nilotinib is that neither of these promising new drugs is effective against leukemia cells harboring the T315I ABL kinase domain mutation. A longer-term concern, especially with advanced CML, is whether clones will inevitably emerge with this mutation and be a harbinger of inevitable drug resistance. Progress in CML drug therapy still continues at quite a remarkable pace: last month in *Blood* the first clinical data on MK-0457,[5] a drug that does seem to be effective against T315I, were published. Other promising agents are in development.

So where do we go next in the drug treatment of CML? Dasatinib is now licensed in many countries and nilotinib may well follow before too long. Other new agents may well become available to prescribers in the next few years. We face some tough challenges: the cost of these new agents is high, presenting considerable difficulties to health funders, patients, and physicians in terms of access to effective treatment. We also need to think carefully about how to use these agents logically in terms of both clinical and cost effectiveness. Comparative studies that address not only efficacy but also quality of life and health economic considerations will certainly be required.

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