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Optimizing tolerability of TKI therapy in CML

Andreas Hochhaus

In this issue of Blood, Kantarjian and colleagues evaluate the safety and tolerability of bosutinib, a new second-generation tyrosine kinase inhibitor (TKI) for treatment of chronic myeloid leukemia (CML) patients in all phases of the disease after failure of initial therapy. The authors propose various measures to avoid and manage side effects associated with the use of the drug.1

Bosutinib is a dual SRC and ABL1 inhibitor with a unique binding mode that accommodates several BCR-ABL1 mutations that confer TKI resistance to imatinib, nilotinib, or dasatinib. In distinction to other inhibitors, bosutinib does not inhibit the platelet-derived growth factor (PDGF) receptors or KIT which might be associated with an individual safety profile.2

The design of the bosutinib phase 1/2 study was complicated by the need to investigate the drug in a population of patients who had failed 2 or 3 prior lines of therapy. However, based on the favorable data presented by Cortes et al and Khoury et al in this journal, bosutinib (500 mg once daily) has been approved by the US Food and Drug Administration and the European Medicines Agency for patients resistant or intolerant to prior therapy. The exact wording of the indication might show some minor differences between the United States and Europe, but there is a new treatment choice available for patients after resistance to initial treatment.3,4

Generally, bosutinib demonstrated acceptable tolerability in patients with Ph+ CML and acute lymphoblastic leukemia, with an adverse event profile distinct from that of imatinib, nilotinib, and dasatinib. Mild or moderate gastrointestinal events and rash were the most common side effects. Cytopenias are usually observed during the initial phase of TKI therapy for Ph+ leukemias. Toxicities observed with bosutinib were manageable with treatment modification and/or concomitant medication.1

However, in the Bosutinib Efficacy and Safety in Newly Diagnosed Chronic Myeloid Leukemia pivotal phase 3 study (BELA trial), testing bosutinib 500 mg once daily vs imatinib 400 mg once daily in first-line use, bosutinib failed to meet the primary end point: the improvement of the rate of complete cytogenetic remission after 12 months of therapy. Many patients were taken off therapy rather early because of toxicity and were not assessed for cytogenetic response. Despite these observations, bosutinib was associated with a superior major molecular response rate after 1 year of therapy (41% vs 27%). Furthermore, rates of transformations, treatment failures, and deaths were all significantly lower in the bosutinib arm.5

Bosutinib has been registered with an initial dose of 500 mg per day with the option to increase the dose to 600 mg per day in case of suboptimal response. This recommended dose was derived from a small phase 1 part of the study in patients after imatinib failure. As in other TKI developments, long-term safety data were not available when phase 2 and 3 studies started.6

For chronic-phase CML patients, a similar situation happened with nilotinib: the recommended second-line dose is 400 mg twice daily but 300 mg twice daily demonstrated better tolerability in first-line use.7 With dasatinib, the initial second-line dose was 70 mg twice daily, but dose optimization trials showed the advantage of 100 mg once daily.8

Most recently, with ponatinib, the daily dose of 45 mg was associated with a high rate of arterial and venous thrombotic events and a dose reduction has been proposed and will be evaluated systematically.9

The only exception for dose adjustments is imatinib: the large randomized German CML IV study demonstrated an improved efficacy of tolerability adapted high-dose therapy in first-line use.10 Initial second-line studies had been performed after failure of interferon α. Such patients, however, do not carry major clones harboring BCR-ABL1 mutations which may require higher doses of imatinib.

All of these observations are based on the different biology of leukemia at diagnosis vs after TKI resistance. The evolution of the disease, in particular, the clonal selection of BCR-ABL1 mutated cells, demands an optimal inhibitory power of the TKI. Thus, in second-line use, acute and chronic side effects might be tolerated and managed with individual measures to achieve best responses. In first-line use, dose should be adapted to reduce or avoid side effects by keeping the best efficacy.

For patients failing imatinib, all 3 second-generation TKIs, including bosutinib, are useful, with ~40% of patients achieving durable complete cytogenetic remission.6 Hence, the analysis and the proposed management recommendations will be of crucial importance for the further use of bosutinib, not only after failure of other TKI, but also for first-line use. Data support the continued clinical development of bosutinib as monotherapy for the treatment of Ph+ CML patients. New studies may reveal an optimized daily dose of the drug reducing the incidence and the grading of side effects. Additional experience with bosutinib will further improve the management of toxicities.

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REFERENCES


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Honing in on the (epi)genetic basis of AITL

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In this issue of Blood, Odejide et al report on recurring mutations in a large series of patients with angioimmunoblastic T-cell lymphoma (AITL) clustering around three epigenetic modifiers: TET2, DNMT3, and IDH2.1

Peripheral T-cell lymphomas (PTCLs) are a heterogeneous group of lymphoid malignancies characterized by innate and early chemotherapy resistance and poor overall outcomes. Among the PTCLs, AITL was first described almost 40 years ago as a poorly defined proliferation of T cells in the setting of immune dysregulation, B-cell proliferation, and adenopathy. Although it is rare overall (2% of lymphomas), AITL is among the top 3 most common subtypes of PTCL, with geographic variation showing increased incidence in Western Europe compared with the rest of the world where it accounts for almost one-third of T-cell lymphomas.2 Neither the etiology nor the rationale for regional variation is known.

AITL is morphologically distinguished from other PTCLs by characteristic diffuse proliferation of small to medium-size neoplastic T cells set in a background of reactive polyclonal cells, including normal CD4+ and CD8+ T cells, B lymphocytes, eosinophils, histiocytes, follicular dendritic cells, and immunoblasts. There is marked vascularity and increased high endothelial venules. Recently, the T-follicular helper (TFH) cell was identified as the normal counterpart of AITL3 with the following immunophenotypic profile: CXCL13+/PD1+, ICOS+, and BCL6+, with occasional CD10 and CD30 positivity. The molecular signature of AITL is dominated by cells within the microenvironment,3,4 and there are several immune suppressive signatures associated with poor outcomes. The clinical outcome is poor overall, with a median survival of approximately 2 years and no specific treatment approach vs other PTCLs. However, up to one-third of patients survive more than 7 years,5 and the biologic differences between long-term survivors and others is not understood.

In this issue of Blood, Odejide et al1 evaluate the coding regions of 219 lymphoma-associated genes in 85 paraffin-embedded tissue samples of AITL in an effort to better characterize its genetic basis. The patients are reflective of most AITL series: advanced median age of 69 years, universally advanced stage, and dismal median survival of 18 months. By using targeted next-generation sequencing, the authors found 80 genes with mutations in the coding region, including 34 genes mutated in more than one patient. In particular, 65 patients (76%) had at least 1 TET2 mutation, and 43 of these patients had more than 1 TET2 mutation. Thirty-three percent of patients had a DNMT3A mutation, and 100% of them also harbored a concomitant TET2 mutation. Seventeen (20%) had IDH2 R172 mutations, and 15 of these patients had concurrent TET2 mutations; this is in contrast to myeloid disorders in which IDH2 and TET2 mutations are thought to be mutually exclusive. In addition to these 3 most common mutations, the authors report a number of gain-of-function and loss-of-function mutations in genes not previously known to be altered in AITL, including TNFSF9, ETV6, CCND3, and STAG3, among others. The significance of these lesser frequency findings is uncertain, particularly whether they are secondary events in subclones or whether they are independently important in the pathogenesis of the disease.

The observation that TET2 and other genes involved in DNA modification are mutated in such a high percentage of patients is noteworthy. TET2 is a member of the ten-eleven translocation (TET) family of genes and plays a crucial role in oxygenation of methylcytosine and DNA demethylation. Loss of TET2 supports its role as a tumor suppressor gene in both myeloid and lymphoid malignancies.6 Given the wide spectrum of affected methylated sites, TET2 proteins thus confer significant epigenetic control over transcription. Although it is more frequently associated with myeloid disorders, TET2 was first noted to be mutated in a handful of lymphoid malignancies, particularly T-cell lymphomas.7 The report by Quiveron et al found that 11.9% of 177 T-cell lymphoma samples and up to one-third of AITL samples had TET2 deletional or insertion mutations. More recently, another group found that TET2 mutations were present in 47% of AITL and 38% of PTCL-not otherwise specified patients but were distinctly absent in other PTCL histologies and seemed restricted to lymphomas with a TFH phenotype.8 Similarly, IDH2 mutations seem restricted to AITL among lymphoid disorders and can be present...
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