populations with environmental exposure to toxic waste. The incidence of MBL ranges from 1% to 18% in these decidedly nonnormal groups. The study by Shim et al, however, is of normal healthy blood donors and not individuals with abnormal findings or a familial or environmental exposure history placing them at increased risk of CLL. Their observation of 7.1% MBL is a better indication of the incidence of MBL in the general population and is consistent with the 7.4% observed in healthy volunteers in Italy. In the current study, gender (male predominance) and age were independent risk factors for MBL, with a 1.4-fold increase in MBL per 10 years' age among men. The incidence of MBL is known to increase with age; a study by Almeida et al indicates that low-count MBL may be present in the vast majority of individuals >70 years old and may be considered a normal finding in this age group. In >96% of the cases, low-count MBL was detected, with the majority having a CLL-like low-count MBL (but 14.8% were atypical or CD5-negative low-count MBL) which may have a different prognosis. A total of 3.4% of the MBL cases were clinical MBL with the associated increased risk of progression to CLL. In addition, 18% of the MBL cases had germline, nonmutated status which may have increased risk of progression to CLL.

The transfer of MBL from donor to recipient has been reported in the setting of allogeneic stem cell transplantation, although this is not comparable to blood transfusion in an immune-competent individual. Furthermore, MBL has not been reported posttransfusion, although there is an increased risk for development of B-cell neoplasia, and in particular CLL, with blood transfusions. In view of the surprisingly common finding of MBL in normal healthy donors, one has to wonder whether there is a potential risk of transfer of a premalignant condition to recipients of blood transfusions, especially in cases of clinical MBL. In addition, the clinical implications of nonmutated status as well as CD5-negative or atypical CLL immunophenotype in low-count MBL are not fully understood and need further clarification. Therefore, the recommendation of Shim et al for a conservative approach to blood transfusions is warranted.

The implications of this study also raise questions concerning screening of donated blood (see figure). Because low-count MBL has minimal or negligible risk of progression, blood from such donors is likely acceptable, but what about clinical MBL? Should donors with a low-level lymphocytosis be screened for MBL, and how would this affect criterion for rejection of donated blood product? Further studies into the possible transference of MBL to blood transfusion recipients are indicated before these questions can be answered. A look-back study at donors of CLL or MBL recipients would be of interest, and the formation of a blood donor clinical MBL cohort for longitudinal study would be equally valuable.

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REFERENCES

Comment on Byrd et al, page 1302

Otlertuzumab more than a TRU(E) toddler in CLL?

Clemens-Martin Wendtner1,2 1KLINIKUM SCHWABING; 2UNIVERSITY OF COLOGNE

In this issue of Blood, Byrd et al present first-in-man data in chronic lymphocytic leukemia (CLL) using otlertuzumab (TRU-016), a fully humanized anti-CD37 protein therapeutic. Although this novel immunotherapeutic shows modest single-agent activity, combinations with phosphatidylinositol-3-kinase (PI3K) inhibitors might open new future perspectives.

CD37 is almost exclusively expressed on mature human B cells and B-cell–derived lymphoid malignancies, arguing for its role as a prime target molecule for CLL immunotherapy. Otlertuzumab, formerly known as TRU-016, is a CD37-specific single-chain, homodimeric therapeutic protein based on modular protein technology; antibody–derived single-chain variable fragments (scFv) specific for CD37 are linked to immunoglobulin constant domains. This small modular immunopharmaceutical (SMIP) is smaller in size compared with classic antibodies and shows higher antibody-dependent cellular toxicity than most recombinant antibodies.

Otlertuzumab was developed by humanizing SMIP-016, a mouse/human chimeric protein that demonstrated antitumor activity against lymphoid malignancies in preclinical studies, including in human B-cell tumor mouse xenograft models.

In this phase 1 study, treatment-naive and pretreated CLL patients received otlertuzumab IV up to a dose of 30 mg/kg per week. Including the dose-escalation and expansion phase of this trial, all together 83 patients were treated. Besides dose-limiting toxicity–relevant hematologic toxicities, including grade 4 neutropenia and thrombocytopenia observed in 4 patients, the
safety profile was quite acceptable. Adverse events included mostly fatigue, nausea, diarrhea, chills, and pyrexia as expected from immunotherapeutics. Although the treatment with oltertzumab seems promising in treatment-naive patients with an 86% response rate, data are quite disappointing in pretreated patients: here, only 17% of them showed an objective response. The low overall response rate of 23% (National Cancer Institute 96 [NCI-96] criteria) or of 20% (International Workshop on Chronic Lymphocytic Leukemia 2008 [IWCLL-2008] criteria including computed tomography imaging), respectively, can be partially explained by the fact that this trial included many high-risk patients (n = 46) harboring a 17p or an 11q deletion or even both.

However, given the fact that frontline therapies in CLL become more and more effective, not only in the younger and fit ones, but also in the elderly and comorbid population, we will probably face more high-risk patients with unfavorable molecular and cytogenetic risk profiles in the relapsed setting in the future.4,5 And to be honest, the competition is overwhelming: small molecules blocking signaling pathways through the B-cell receptor (BCR), that is, Bruton tyrosine kinase (BTK) and PI3K inhibitors, seem to be much more powerful compared with oltertzumab. These small molecules seem to work regardless of the numbers of pretreatments and irrespective of the genetic or molecular risk parameters. The BTK inhibitor ibrutinib and the PI3Kδ inhibitor idelisib easily induce remissions in roughly three-quarters of relapsed/refractory patients with CLL.6,7 As if that is not enough, inhibitors of the BCL-2 protein family also broaden the spectrum of weapons in the attack against CLL cells. ABT-199, a highly potent, orally bioavailable, and BCL-2-selective inhibitor has shown promising data in CLL patients with high-risk cytogenetic aberrations and/or fludarabine-refractory disease.8 Nowadays, modern trials try to answer the question of whether a combination of these classes of drugs, especially also combined with monoclonal antibodies, might be even more beneficial for the patient, not only in the relapse setting. And just to make the picture more complete and to mention other competitors in the field of immunotherapeutics: we all have followed up on innovations like chimeric antigen receptors with specificity for the B-cell antigen, coupled with sophisticated CD137 and CD3-ζ signaling domains.9

Given these amazing developments in the last few years in the field of CLL, oltertzumab (TRU-016) seems to be more a true toddler, at least in the monotherapy setting. But a closer look on the mode of action might open a window of opportunity for this second-generation immunotherapeutic. Upon ligation by SMIPs like oltertzumab, the CD37 molecule initiates events resulting as a net effect in apoptosis, but in this context, 2 opposing mechanisms by different tyrosine residues of CD37 have recently been elucidated: on the one hand, an immunoreceptor tyrosine-based inhibitory–like motif fosters recruitment of the proapoptotic phosphatase SHP1, and on the other hand, an immunoreceptor tyrosine-based activation motif enhances counteracting prosurvival signals via mediating PI3K-dependent survival. Therefore, a combination of oltertzumab with blockade of PI3K signaling could shift this balance and enhance the proapoptotic axis (see figure). This seems much more rational than just combining an immunotherapeutic with classic cytotoxic drugs or just another monoclonal antibody. Whether this indeed would result in synergistic clinical outcomes in favor of the individual patient with CLL has to be tested, but rather soon. This could further pave the road for a chemo-free treatment of CLL thus combining modern small molecules like BCR inhibitors and next-generation immunotherapeutics like SMIPs.

Conflict-of-interest disclosure: The author declares no competing financial interests.

REFERENCES
8. Souers AJ, Levenson JD, Boghaert EB, et al. ABT-199, a potent and selective BCL-2 inhibitor, achieves...
Comment on Kantarjian et al, page 1309

Optimizing tolerability of TKI therapy in CML

Andreas Hochhaus1

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 cyto genetic 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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Clemens-Martin Wendtner