Comment on Schwamb et al, page 3978

Drug sensitivity and sphingolipid metabolism in CLL

Ulrich Jaeger  MEDICAL UNIVERSITY OF VIENNA

In this issue of Blood, Schwamb and colleagues describe a novel mechanism of action through which kinase inhibitors can overcome B-cell receptor (BCR)–mediated survival of chronic lymphocytic leukemia (CLL) cells via their influence on sphingolipid metabolism.1

Management and outcome of patients with CLL have changed during the past decade due to improvements in molecular diagnostics and the implementation of targeted drug therapy.2,3 This rapid progress was due to the discovery of chromosomal changes, the understanding of the prognostic impact of the mutational status of immunoglobulin heavy chain genes, the discovery of prognostic markers and potential therapeutic targets by gene expression profiling, and recently by sequence analysis of the CLL genome.4 We have learned that CLL cell survival is strongly influenced by interaction with the microenvironment through cell-to-cell contact or via soluble factors and surface receptors. The central molecule in this cross-talk is the BCR composed of immunoglobulin heavy and light chains.5 The BCR ensures survival of B-cells by transduction of external stimuli to the inner cell through an elaborate signaling pathway (see figure). BCR-related genes and proteins are constantly stimulated in bone marrow and lymph nodes of patients with CLL.6

Contact of the BCR with an antigen (or in the experimental setting an anti-IgM antibody) triggers a cascade of events including calcium influx, concerted association of proteins at the intracellular BCR portion, protein phosphorylation, activation of transcription factors, and integrins. Constant antigenic stimulation of the BCR is thought to be driving leukemia development.7 BCR activation results in enhanced cell survival, proliferation, and cellular adhesion making this pathway an interesting target for antileukemic therapy. Specific inhibition of 2 kinases associated with BCR activation (phosphatidylinositol-3-kinase, PI3K, and Bruton tyrosine kinase, BTK) has recently shown impressive clinical results.8,9

Changes in lipid metabolism associated with immunoglobulin mutation status have previously been observed.10 The novelty of the paper by Schamb et al lies in the description of the functional modulation of sphingolipid metabolism in CLL cells as a consequence of BCR stimulation, linking this process to potential therapeutic applications.1 The authors have investigated changes in the intracellular ratio between ceramide and glucosylceramide on BCR stimulation in primary CLL cells. The proapoptotic ceramide is converted to the antiapoptotic glucosylceramide by the enzyme UDP-glucose ceramide glucosyltransferase (UGCG). Direct inhibition of UGCG induces chronic lymphocytic leukemia (CLL) cell apoptosis. The kinase-specific inhibitors GS-1101 (PI3K) and ibrutinib (BTK) also cause down-regulation of UGCG leading to restoration of the ceramide:glucosylceramide equilibrium and leukemic cell death. This constitutes a novel mechanism of drug action. In addition, this effect on sphingolipid metabolism sensitizes the cells for mitochondria-targeting drugs such as ABT-737. Figure adapted from Schwamb et al; see Figure 6 in the article that begins on page 3978.

Modulation of the ceramide:glucosylceramide equilibrium by B-cell receptor (BCR) signaling and the novel kinase inhibitors GS-1101 and ibrutinib in CLL. BCR stimulation by antigens (Ags) or anti-IgM results in a shift from ceramide (proapoptotic) to glucosylceramide (antiapoptotic) mediated by up-regulation of UDP-glucose ceramide glucosyltransferase (UGCG). Direct inhibition of UGCG induces chronic lymphocytic leukemia (CLL) cell apoptosis. The kinase-specific inhibitors GS-1101 (PI3K) and ibrutinib (BTK) also cause down-regulation of UGCG leading to restoration of the ceramide:glucosylceramide equilibrium and leukemic cell death. This constitutes a novel mechanism of drug action. In addition, this effect on sphingolipid metabolism sensitizes the cells for mitochondria-targeting drugs such as ABT-737. Figure adapted from Schwamb et al; see Figure 6 in the article that begins on page 3978.
the BTK inhibitor ibrutinib (PCI-32765). It is unclear if this is a direct effect or mediated by kinase inhibition. Sphingolipids are also known as mediators of mitochondrial apoptosis. Consistent with the antiapoptotic effect of glucosylceramide, BCR stimulation reduced the effect of the mitochondria-targeting drug ABT-737. Concomitant treatment with low doses of the kinase (and apparently UGCG) inhibitors GS-1101 and ibrutinib restored the activity of ABT-737 leading to C.L.L. cell death. Thus, the 2 drugs may also be regarded as sensitizers for ABT-737, opening up the possibility for novel drug combinations.

The discovery adds novel aspects to our understanding of BCR function as well as the potential implications for drug therapy. It will help to explain changes in (sphingo-/) lipid metabolism as well as BCR-triggered gene regulation in C.L.L. This opens up a whole new approach for treatment options, the mechanism of action and functional downstream effects of novel kinase inhibitors as well as many other drugs that act on the BCR or one of its signaling pathway components. C.L.L. therapy continues to be a success story.

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

REFERENCES


Comment on Radich et al, page 3898

CML: the good, the better, and the difficult choices

Jorge Cortes MD Anderson Cancer Center

In this issue of Blood, Radich and colleagues from 4 cooperative groups report on the results of a randomized study of dasatinib versus imatinib as initial treatment for patients with chronic phase chronic myeloid leukemia (CML).1 This study is the sequel to a trial where they first compared imatinib standard-dose to imatinib high-dose. The results of the second portion of the study presented here show an improved outcome for patients receiving therapy with dasatinib compared with standard-dose imatinib. The rate of complete cytogenetic response was 84% with dasatinib and 69% with imatinib, and the rate of 3-log reduction of transcripts at 1 year was 59% versus 44%, respectively. With a median follow-up of 3 years, no differences in progression-free survival or relapse-free survival were identified, perhaps due to the small number of events in either arm.

These results confirm previous observations using second-generation tyrosine kinase inhibitors (TKIs; dasatinib, nilotinib or bosutinib) as initial therapy for chronic myeloid leukemia (CML).2-4 The study by Radich et al has the merit of providing an independent confirmation of data obtained mostly through industry-sponsored studies. The results have been very reproducible: second-generation TKIs provide a higher rate of responses and responses occur earlier, with a trend toward a decreased rate of transformation to accelerated or blast phase. Other unfortunate conclusions are also shared. One of great concern is the high rate of early treatment discontinuation reported in all of these studies. The present study reports that 20% of patients treated with imatinib and 28% with dasatinib discontinued therapy within 12 months.1 Rates reported at approximately the same follow-up time from other trials are 19% to 21% for imatinib, 16% to 18% for nilotinib,5 16% for dasatinib,6 and 28% for bosutinib.7 With longer follow-up, rates have increased to 23% for dasatinib5 and 22% to 26% for nilotinib.6 These rates are surprising considering the improved efficacy and generally favorable toxicity profile of the new agents compared with imatinib. It is possible that the availability of a greater menu of treatment options is leading to a trend toward changing therapy too soon without full evaluation of efficacy or management of mild to moderate adverse events through therapeutic interventions and/or dose adjustments. It will be important, as these drugs are being used more frequently as initial therapy, that we use the agent of choice to its full potential and avoid quick transition from one drug to another for questionable indications.

A frequent question now is whether results such as the ones reported here mean that all patients should be treated with a second-generation TKI. Taken at face value, we should always aim in cancer treatment to use our best agent first to have the best chance of rendering our patient free of disease for the longest time, and cured if possible. Our first shot is always our best shot. Nonetheless, one cannot disregard some important facts: (1) most patients do well with imatinib, (2) most patients with resistance to imatinib are still in chronic phase and in generally good condition, and (3) many patients with resistance to imatinib respond to second-generation TKIs. If one adjusts for the sequential use of effective therapy, the current event-free survival is 88% at 7 years compared with the unadjusted rate of 81%.7 However, only 40% to 50% of patients with resistance to imatinib achieve a complete cytogenetic response with second-generation TKIs.8-10 With growing awareness of the relevance of early
Drug sensitivity and sphingolipid metabolism in CLL

Ulrich Jaeger