Chronic Lymphocytic Leukemia: New Concepts for Future Therapy

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Abstract

Over the past several years, we have witnessed rapid advances in our understanding of the biology and treatment of chronic lymphocytic leukemia (CLL). New prognostic factors have been characterized that help identify patients at high risk of rapid disease progression, refractoriness to treatment, and short overall survival (OS). These advances have led to a significant paradigm shift in the management of CLL. Novel therapeutic strategies, including combinations of monoclonal antibodies with conventional chemotherapy, have dramatically improved response rates, remission duration, and recently, OS. However, these benefits do not appear to extend to certain patient subsets, especially those with unfavorable clinical or cytogenetic risk factors. The majority of patients with CLL will invariably relapse following first-line therapy and can acquire high-risk genetic abnormalities. Repeated treatment leads to eventual therapeutic refractoriness and shortened survival compared with age-matched healthy individuals. Several novel agents and strategies, including next-generation anti-CD20 monoclonal antibodies, the alkylating agent bendamustine, the immunomodulatory agent lenalidomide, the cyclin-dependent kinase inhibitor flavopiridol, and small-molecule Bcl2 inhibitors, are currently under clinical investigation as novel agents that will hopefully improve treatment outcomes for CLL. Though allogeneic stem cell transplantation offers curative potential, it also presents clinical challenges in terms of patient appropriateness, donor availability, and timing. The merits and challenges of incorporating these treatment modalities into the treatment algorithm for patients with CLL, as discussed by a panel of experts in CLL, are outlined in this article.

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Introduction

The first panel of global experts in chronic lymphocytic leukemia (CLL) was convened on December 3, 2009, in New Orleans, LA for a timely discussion on several topical issues including advances in biology and the identification of new targets for drug discovery, the role of transplantation, current data with emerging agents/strategies, and how these might be integrated into the treatment continuum for CLL. The proceedings from this workshop are summarized here by session topic.

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New Biology of Chronic Lymphocytic Leukemia: Translation Into New Targeted Therapies

The anti-CD20 monoclonal antibody (MoAb) rituximab and the anti-CD52 MoAb alemtuzumab are widely used in the treatment of CLL, and have led to dramatic changes in the therapeutic landscape of the disease; both are approved for use by the European and/or United States regulatory agencies.[1] However, CD20 and CD52 are not exclusively expressed by CLL cells, potentially resulting in the elimination of normal B and T lymphocytes, leading to increased treatment-related toxicities. Particularly, CD52 is ubiquitously expressed on lymphocytes, macrophages, monocytes, and eosinophils, and the anti-CD52 MoAb alemtuzumab has been associated with profound immune suppression, potentially leading to reactivation of latent viruses and development of opportunistic infections.[2-4] Recent data also show expression of CD52 on neu-

trophils, thus offering a possible explanation for alemtuzumab-associated neutropenia.[5] The immune suppressive effects of both MoAbs and purine analogues has motivated the identification of new important pathways and more specific therapeutic targets in order to identify therapeutically active agents with reduced toxicities and immune suppression.

Current evidence in human cancers suggests that combinations of MoAbs with conventional cytotoxic drugs maximize therapeutic potential based on synergy.[6] This is best exemplified in hematologic malignancies in that rituximab significantly improves clinical outcome when combined with fludarabine and cyclophosphamide (FCR) compared with chemotherapy alone (FC) in younger fit patients with CLL.[7,8] Toxicities—particularly myelosuppression—associated with the FCR regimen limit its universal application to all patients, further underscoring the need for new therapeutic agents. The focus of this workshop session was to identify new and unique surface molecules on CLL cells and signaling pathways that could be targeted for therapeutic intervention.

Chronic lymphocytic leukemia is characterized by the accumulation of predominantly quiescent malignant cells with pathogenetic deficiencies in cell death mechanisms, though it is driven by proliferation as well.[9-11] Multiple defects in the apoptotic machinery and response to dysregulated survival signals from the microenvironment are critical for CLL cell survival and disease progression. Phosphatidylinositol 3-kinase (PI3K)/Akt signaling, the p53 pathway, and chemokine- and cytokine-activated receptors were identified as key pathways implicated in the survival of CLL cells and, possibly, their resistance to chemotherapy-induced apoptosis. The elucidation of mechanisms that confer a selective survival advantage to CLL cells is of paramount importance in order to identify and develop targets for therapeutic intervention. Specifically, the orphan receptor tyrosine kinase ROR1, stereotyped B-cell receptors (BCRs), and the PI3K/Akt signaling pathway were highlighted for discussion.

ROR1 was identified in CLL-specific gene signatures derived from 2 independent gene expression profiling studies in B-cell malignancies and normal B cells. The ROR1 protein is constitutively expressed on CLL cells and not expressed on normal B cells, and may be independent of normal B-cell activation, suggesting that ROR1 might prove to be a more specific CLL marker than other cell surface antigens such as CD20 that are currently being targeted.[12,13] Preclinical evidence also suggests a role for ROR1 in the survival of CLL cells, thus functionally linking it to CLL cell biology.[14] Although the level and consistency of ROR1 expression and antibody-binding capacity of ROR1 on CLL cells was found to be relatively lower than CD20, its selective expression on CLL cells and homogeneous expression in different patient samples might allow ROR1 MoAb targeting.[15] Moreover, antibody binding may lead to active internalization of a portion of surface ROR1, with potential implications for the development of drug-conjugated MoAbs.[15]

Stereotyped B-cell receptors have been identified in approximately 20% of patients with CLL based on extensive overlap in BCR structure and specificities, and are characterized by preferential nonrandom combinations of immunoglobulin heavy chain variable genes (*IGHV*) and heavy-chain complementarity determining region-3 (HCDR3).[16,17] Because approximately 10 CLL-biased stereotyped BCR subsets currently account for 80% of all of the expressed stereotyped receptors in CLL, it is hoped that one or more of these receptors might conceivably serve as a target for treatment. Moreover, the predominant association of stereotyped *IGHV* with the unmutated *IGHV* phenotype might potentially allow targeting of a poor-prognosis subgroup of patients in CLL.

The microenvironment-leukemia cell exchange in CLL, the migration of leukemia cells and adhesion to stromal cells, is largely mediated by chemokines secreted by stromal cells and interaction with their respective receptors such as CXCR4 on leukemia cells. Downstream signaling involves multiple pathways, including the PI3K/Akt pathway and ultimately the microenvironment provides a niche for CLL cells that is thought to be protective from chemotherapy. Chemokine CXCR4 antagonists have been shown to restore the sensitivity of CLL cells to chemotherapy in experimental studies, which subsequently led to the clinical evaluation of the small-molecule CXCR4 antagonist plerixafor in CLL.[18,19] Recognizing that targeting CLL-microenvironment interactions might be necessary to overcome stromal cell–mediated effects, recent investigative efforts have focused on the PI3K pathway. Although the PI3K/Akt signaling pathway is constitutively activated in CLL and implicated in facilitating antiapoptotic signals downstream of the BCR, the lack of specific inhibitors possessing sufficient activity and bioavailability has precluded their clinical development in CLL.[20,21] However, the recent availability of specific inhibitors of this signaling cascade has generated renewed interest in this pathway.[22] In preclinical studies, isoform-selective PI3K inhibitors targeting different isoforms of the p110-kDa catalytic subunit of PI3K have been shown to antagonize stromal cell–derived migration and survival of CLL cells.[23] Of these, the p110δ isoform is specific to hematopoietic cells, and might serve as an attractive target. CAL-101, a selective inhibitor of the PI3K p110δ isoform, is currently in clinical testing and has shown clinical benefit in CLL; dose-limiting toxicity is manifested by elevations in liver enzymes.[24] A multicenter trial is evaluating CAL-101 in combination with rituximab and bendamustine in CLL.[25]

Two molecules that belong to the tumor necrosis factor (TNF) superfamily, BAFF (B-cell–activating factor belonging to the TNF family) and APRIL (a proliferation-inducing ligand), and their receptors have emerged as key regulators of CLL cell survival.[26] Receptors for BAFF and APRIL are expressed on CLL cells, and when ligated by BAFF and APRIL can promote CLL cell survival. BAFF and APRIL are released by nurse-like cells of the microenvironment in a paracrine manner or by CLL cells themselves in an autocrine manner.[26] Activation of both the canonical and noncanonical NF-κB pathways by BAFF, and the selective activation of the canonical pathway by APRIL are critical for CLL cell survival.[27] Although inhibition of the canonical NF-κB pathway with inhibitors to components of the pathway or BAFF and APRIL was initially proposed, it was cautioned that the role of this pathway in several cellular processes might prohibit that possibility; blocking downstream effectors of this pathway might be more practical. However, a fusion protein targeting both BAFF and APRIL is in early clinical development with recent data from a phase IB trial reporting acceptable tolerability.[28]