enzyme is overexpressed in CLL B lymphocytes compared with normal B lymphocytes and, more importantly, the activity of this enzyme is higher in leukemic lymphocytes. Although not done, because the recombinant protein is available, a serial dilution of this protein will allow for quantitation of the exact amount of PI3Kδ isoform in normal and malignant lymphocytes. The group introduces us to a selective inhibitor of this isoform, CAL-101. It is not clear whether the expression level of this protein is correlated with the biological effect of CAL-101, as T lymphocytes that express high levels of this protein were not affected by this agent. Compared with the direct biological effect of CAL-101 on CLL lymphocytes (which was marginal), the impact on cytokine production of T and NK cells was impressive and was consistent with the role of PI3Kδ in T-cell cytokine production. The mechanism for this effect, however, was not explored and remains elusive.

The authors identify mechanism of CAL-101–induced CLL cell death; they show a decrease in Akt phosphorylation, which occurs through the PI3K pathway. In addition, it inhibited phosphorylation of GSK3β. These signaling pathways are associated with Mcl-1 stability and may have been responsible for a decrease in Mcl-1 protein levels in CLL cells and cell death after CAL-101 treatment. Furthermore, CAL-101 disrupted interactions of CLL cells with microenvironment stimuli.

The obvious question, which arises from these preclinical investigations with a variety of kinase inhibitors, is their efficacy in the clinic. Although these are early investigations, recent clinical trials suggest that these agents have potential. With the first clinically used BTK inhibitor, fostamatinib (which is a prodrug of R406), a response rate of 55% was achieved in previously treated small lymphocytic leukemia (SLL)/CLL (n = 11). Similarly, recent clinical results with PCI-32765, a small-molecule BTK inhibitor, resulted in complete response and 8 partial responses in 13 CLL/SLL patients with a pharmacodynamic end point suggesting occupancy on BTK by the drug. Pim kinase inhibitor has not been evaluated in patients with CLL, but the first clinical investigation is ongoing (http://www.cancer.gov/search/ViewClinicalTrials.aspx?crid=637010&version=HealthProfessional&protocolsearchid=7912622). Finally, phase 1 studies in relapsed/refractory hematologic malignancies with oral CAL-101 resulted in a 30% overall response rate in CLL (n = 33). The pharmacokinetic and pharmacodynamic investigations demonstrated biologically required concentrations of the drug (1–7 μM) with a decline in phosphoAkt in targeted pathogenic B lymphocytes.

In conclusion, as opposed to conventional cytotoxic chemotherapy, pathophysiology of CLL lymphocytes and their interactions with the microenvironment milieu offer untested opportunities to tailor therapeutic options for patients with CLL. Understanding of the molecular and cellular biology of CLL, albeit at infancy stage, has provided novel kinase targets (previously allied to CML) to change the therapeutic strategies for this B-cell lymphocytic neoplasm.

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REFERENCES

Comment on Coiffler et al, page 2040

A decade of R-CHOP

Laurie H. Sehn BRITISH COLUMBIA CANCER AGENCY

Initial results of the first randomized trial evaluating the addition of rituximab to CHOP for DLBCL were reported in December 2000, ushering in the new millennium by delivering on the promise of targeted therapy. In this issue of Blood, Coiffler et al—having reached a median follow-up of 10 years—confirm a sustained survival benefit and a cure rate for elderly patients that is over the 50th percentile with the simple addition of a monoclonal antibody targeting CD20 to the “gold standard” chemotherapy. The magnitude of this advance cannot be overstated, as the intergroup trial comparing third-generation regimens to CHOP demonstrated that the limits of chemotherapy alone had apparently been reached.

With R-CHOP (rituximab–cyclophosphamide, doxorubicin, vincristine, and prednisone), the 10-year progression-free and overall survival rates for elderly patients with advanced-stage diffuse large B-cell lymphoma (DLBCL) are 36.5% and 43.5%, respectively.
respectively, an absolute improvement of approximately 16% over CHOP alone. Only 39.5% of patients developed disease progression and the majority of patients remain alive and well or have died from unrelated causes. Importantly, longer follow-up has not unveiled any unexpected toxicities. Rates of secondary cancers were similar between the 2 cohorts, as were deaths from treatment toxicity. More patients in the R-CHOP cohort had the opportunity to die from unrelated diseases, but no particular pattern emerged. Although the long-term safety profile of rituximab in this setting appears favorable, ongoing vigilance is required. The current study by Coiffier et al represents only a moderate number of patients, many of whom have a limited life expectancy due to advanced age. Long-term safety monitoring in younger patients remains important and in the setting of extended administration of rituximab where prolonged immunosuppression may increase the likelihood of delayed toxicities.

Although outcomes in DLBCL have dramatically improved with R-CHOP, there remains room for improvement. Nine percent of patients on the LNH-98.5 trial progressed during primary therapy and overall approximately one-third of patients developed progressive disease within 3 years. Coiffier and colleagues also highlight the risk of delayed relapse, as 10% of all progressions in the R-CHOP cohort occurred beyond 5 years. Elderly patients who fail R-CHOP continue to have a poor outcome, with a median survival after progression of 0.7 months. However, some patients did achieve prolonged survival with salvage therapy. Interestingly, the outcome after progression appeared slightly better in patients who received R-CHOP, in contrast to what has been reported in younger transplant-eligible patients treated on the CORAL study. This result may in part be explained by the fact that a higher proportion of patients in the R-CHOP cohort experienced a delayed relapse which was associated with prolonged survival after progression, as well as the greater availability of rituximab with salvage therapy over time.

It took 40 years to improve upon CHOP, and 1 decade into R-CHOP it seems appropriate to ask whether further progress has been made. Certainly, we have gained greater biologic insight into the heterogeneity of DLBCL. The most recent edition of the World Health Organization classification of lymphoma recognizes a large category called “DLBCL, not otherwise specified” which includes various morphologic, immunohistochemical, and molecular subgroups, and separately recognizes an increasing number of distinct subtypes of large cell lymphomas. Gene expression profiling studies have identified at least 2 distinct molecular subtypes of DLBCL: NOs, germinal center B cell–like (GCB) and activated B cell–like (ABC), which rely on different pathways of oncogenesis. Future clinical trials will need to take this information into account, particularly when evaluating targeted agents which may selectively benefit individual subtypes. This concept was highlighted by a recent study investigating the addition of bortezomib to DA-EPOCH for relapsed DLBCL, which suggested a benefit in patients with the ABC, but not the GCB, subtype.7

Improved outcomes in DLBCL also pose a challenge for the development of future clinical trials, as larger numbers of patients will be required to demonstrate further incremental benefits. Care must be taken not to inappropriately deviate from established curative therapy or to add needless toxicity to those who would otherwise be cured with R-CHOP alone. Accurate prognostication will be vital to enable tailored therapy approaches. Although the International Prognostic Index remains useful, it has limited ability to identify patients with very poor outcome and does not provide biologic insight. Multiple biologic predictors appear promising; however, none have been validated for routine clinical use.9 Similarly, the merit of midtreatment positron emission tomography (PET) scanning in DLBCL remains controversial. Further investigation of potential prognostic and predictive markers in the context of prospective clinical trials will be necessary before establishing their generalized use.

Thus far, a successor to R-CHOP has not been identified. Recently, a large randomized trial of R-CHOP and bevucizumab was stopped prematurely due to excessive cardiac toxicity. Two trials evaluating R-CHOP-14 (R-CHOP administered at a 2-weekly interval) have been completed, although interim results have not confirmed a benefit.10 Many additional clinical trials are under way or being planned. These include the evaluation of alternative chemotherapy regimens, such as R-ACVBP and DA-EPOCH-R; the addition of enzastaurin (a PKC-β inhibitor) as maintenance therapy; the use of newer generation CD20 monoclonal antibodies; and tailored strategies based on interim PET scanning. As we eagerly await results from the next generation of trials, the long-term results of LNH-98.5 should inspire optimism that progress is achievable.

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REFERENCES


A decade of R-CHOP

Laurie H. Sehn