form of hemoglobin in the mouse. A similar conclusion regarding the marked differences in gene expression between human and mouse erythropoiesis has also been reached by an independent analysis of previously published gene expression data of human and mouse erythroblasts isolated by flow cytometry.1,6

These marked differences in mouse and human erythroid transcriptomes are surprising given the morphological similarities that occur in both species to ultimately form a biconcave disc containing mostly hemoglobin. There certainly can be different pathways that achieve the same end result. However, a caveat of both studies is that the mouse erythroblasts were isolated directly from the bone marrow, whereas the human erythroblasts were derived from prolonged in vitro culture of neonatal or adult CD34-positive cells that mature as a cohort. Because mammalian erythroblasts normally mature attached to macrophage cells within erythroblastic islands, it remains to be determined how many of the species-specific differences in gene expression might be due to the in vitro microenvironment of the cultured human erythroblasts.

Most studies of global erythroid gene expression have relied on chip-based technologies. A significant strength of this study is the use of RNA-Seq (RNA Sequencing) to generate the gene expression data. For example, this approach has now permitted the global analysis of ribosomal genes, which surprisingly make up a significant proportion of the most abundantly expressed genes present in human proerythroblasts and basophilic erythroblasts. In addition, this approach offers the possibility of analyzing the expression of splice variants, including the identification of novel erythroid-specific variants, as well as noncoding RNAs during erythroid maturation. Such analyses of these databases are eagerly awaited and should certainly lead to new insights regarding the regulation of human erythropoiesis, as well as that of its closest model organism.

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

REFERENCES

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Comment on Flinn et al, page 3406; and Kahl et al, page 3398; and Brown et al, page 3390

CLL and NHL: the end of chemotherapy?

Bruce D. Cheson GEORGETOWN UNIVERSITY HOSPITAL

“The times they are a changin’”—Bob Dylan

In this issue of Blood, Flinn et al, Kahl et al, and Brown et al provide further encouragement that the possibility of a chemotherapy-free world is, indeed, a rapidly approaching reality in indolent non–Hodgkin lymphomas (NHLs), mantle cell lymphoma (MCL), and chronic lymphocytic leukemia (CLL).1-3

The therapeutic holy grail for lymphoid malignancies has long been an effective chemotherapy-free strategy to avoid the scourge of the nonspecific toxic drugs that patients have been subjected to for decades, such as anthracyclines, alkylating agents, vinca alkaloids, and purine analogs. Initial forays into the nonchemotherapy realm included single-agent rituximab,4 doublets of monoclonal antibodies,5,6 or rituximab combined with the immunomodulatory agent lenalidomide.7 Each of these well-tolerated regimens produced high response rates with durable remissions. Nevertheless, the diseases remain incurable. Recent interest has focused on a series of agents that inhibit intracellular pathways that promote the proliferation and survival of malignant lymphocytes. Several of these pathways are activated through B-cell receptor signaling (see figure). One of the first such drugs was fostamatinib disodium, a spleen tyrosine kinase inhibitor that exhibited only modest activity and is not being actively pursued in lymphoid malignancies.8

More recently, idelalisib (formerly known as CAL-101 and GS-1101) has induced considerable interest. This potent, highly selective, orally bioavailable small molecule inhibits the δ isozyme of phosphatidylinositol 3-kinase (PI3K), a pathway that is overactive in a number of lymphoid malignancies as well as solid tumors. PI3K exists in 4 different isoforms: p110α, β, γ, and δ, the last being most relevant to B lymphocytes. As described in each of the 3 articles, PI3K-α-mediated phosphorylation activates the serine/threonine kinase AKT and, subsequently, mammalian target of rapamycin (mTOR). Overexpression of PI3K/AKT appears to contribute to the pathogenesis of various lymphoid malignancies, including indolent NHL, MCL, and CLL. Inhibiting PI3K results in cell death through apoptosis.

Rarely have we encountered enthusiasm for drugs such as that for idelalisib, which is based on phase 1 data. Flinn et al1 administered idelalisib to 64 heavily pretreated patients with indolent NHL, more than half of whom were refractory to previous chemotherapy. The response rate was 47%, but it was 69% in those treated at the now accepted dose of ≥150 mg twice daily, with a median progression-free survival (PFS) of 16.5 months at this dose level. These data have been confirmed in a subsequent phase 2 trial.9 Kahl et al2 treated 40 patients with MCL, with a response rate of 69% at a dose of ≥150 mg
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REFERENCES


6. Grant BW, Jung SH, Johnson JL, et al. A phase 2 trial of extended induction epratuzumab and rituximab for refractory MCL and CLL, and, hopefully, idelalisib will follow suit in short order. At that point, how do we decide which of these active agents to choose (if they are comparably priced)? Other than some differences in toxicity profile that may determine eligibility in a subset of patients (eg, coagulation abnormalities with ibrutinib, hepatic dysfunction with idelalisib), it may take comparative studies or biomarker assays to help us select appropriately. However, for now, we can provide our patients with new, effective, and less toxic treatment options for their diseases, and even more importantly, we can also provide hope that better treatments are still ahead. Although as single agents, these exciting drugs can transform indolent NHL, MCL, and CLL into more acceptable chronic disorders, it is quite possible that rational combinations will eventually lead to cure of these incurable diseases.

Conflict-of-interest disclosure: B.D.C. is a consultant for and has received research support from Gilead, Pharmacyclics/Janssen, and Roche-Genentech.

Cite this article as Brown et al. reported on 54 patients with correlated with the extent of prior treatment. 

Twice daily, with a PFS of 3.7 months that correlated with the extent of prior treatment. Brown et al.1 reported on 54 patients with heavily pretreated, relapsed, or refractory CLL, many with adverse features. They demonstrated that idelalisib inhibited PI3Kδ, impairing Akt phosphorylation in patient CLL cells, significantly reducing serum levels of CLL-related chemokines and cytokines. When administered twice daily, idelalisib induced responses in 72% of patients, including 53% of those with 17p- and/or tumor protein 53 gene mutation, generally considered among patients with the most unfavorable prognoses. The overall median PFS was 32 months when using the currently recommended dose. Common to these 3 trials was a rapid tumor reduction with some responses lasting up to 2 years, and a favorable toxicity profile with the most prominent adverse effects being diarrhea, nausea, fever, fatigue, and an asymptomatic reversible transaminitis.

We are fortunate to have an increasing number of active oral drugs for patients with these diseases, including the Bruton tyrosine kinase inhibitor ibrutinib, the PI3Kδ/γ inhibitor IPI-145, the BCL-2 inhibitor ABT-199, and those that target programmed death-1/programmed death ligand-1, among others.

However, despite the high response rates with each of them, most remissions are partial and, currently, these agents are administered as long as response and clinical and financial tolerance persist (they are expected to be quite unconscionably expensive). Those factors together have led to numerous trials to improve on their efficacy and limit the duration of treatment, such as combining them with other drugs, resulting in a better quality of response. A common backbone for ongoing clinical trials has been bendamustine plus rituximab. However, a more interesting avenue of investigation is combining them with other biologic agents. In a recent study, rituximab plus idelalisib achieved a survival benefit compared with rituximab alone in relapsed/refractory CLL patients with comorbidities. Other trials are exploring the additive benefit of these agents to the combination of rituximab-lenalidomide, such as those being piloted by the Alliance (formerly Cancer and Acute Leukemia Group B) with idelalisib in relapsed MCL or follicular lymphoma, and with ibrutinib as initial treatment of follicular lymphoma. Combinations of kinase inhibitors with each other or with proapoptotic agents are also of interest.

Ibrutinib is already approved by the US Food and Drug Administration for relapsed/refractory MCL and CLL and, hopefully, idelalisib will follow suit in short order. At that point, how do we decide which of these active agents to choose (if they are comparably priced)? Other than some differences in toxicity profile that may determine eligibility in a subset of patients (eg, coagulation abnormalities with ibrutinib, hepatic dysfunction with idelalisib), it may take comparative studies or biomarker assays to help us select appropriately. However, for now, we can provide our patients with new, effective, and less toxic treatment options for their diseases, and even more importantly, we can also provide hope that better treatments are still ahead. Although as single agents, these exciting drugs can transform indolent NHL, MCL, and CLL into more acceptable chronic disorders, it is quite possible that rational combinations will eventually lead to cure of these incurable diseases.

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Cite this article as Brown et al.
Comment on Matsumoto et al, page 3429

p57Kip2 regulates T-cell development and lymphoma

Senthil Raja Jayapal1 and Philipp Kaldis1,2

INSTITUTE OF MOLECULAR AND CELL BIOLOGY; NATIONAL UNIVERSITY OF SINGAPORE

In this issue of Blood, Matsumoto et al report that T cell–specific deletion of the cyclin-dependent kinase inhibitor p57Kip2 (p57) in mice leads to a block in T–cell development as a result of hyperactivation of the E2F-p53 pathway and demonstrate that the loss of p57 accelerates lymphomagenesis in the absence of p53.1

The p57-E2F1-p53 pathway in thymocyte development and lymphomagenesis. p57 regulates E2F1 to control E2F target gene expression and p53 activity during normal thymocyte development. In the absence of p57, increased E2F target expression and p53 hyperactivation contribute to the arrest of thymocyte development at the DN3 to DN4 transition. The developmental arrest of thymocytes lacking p57 is partially rescued by the loss of E2F1. Loss of p53 in thymocytes lacking p57 leads to acceleration of thymic lymphoma development, suggesting that the observed p53 hyperactivation in the absence of p57 executes an important tumor suppressor function in thymocytes. Professional illustration by Marie Dauenheimer.
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