As with all important research there are many questions raised by the work of Rossi and colleagues. It will also be important to characterize the independent impact of miR-21 expression in models including 17p and TP53 mutation. Before translating the results into clinical practice, it will be important to confirm the impact of the deregulated miRs in a uniformly treated cohort; ideally, this should be done with purified CLL samples derived from a prospective trial. This is particularly important as the follow-up is relatively short (20 months) and the cohorts studied diverse.

Although the current work does not attempt to identify the basis for the association between miR-21 expression and outcome, the authors hint at some potential targets. It will be important to understand the function of these miRs and, particularly, how they relate and depend on functional p53. A first step toward this goal will be the detailed characterization of not only 17p status, but also TP53 mutation.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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CLINICAL TRIALS

Comment on Lukina et al, page 893

The substrate is down: is the IV out?

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The effectiveness of a new substrate reduction agent (eliglustat tartrate) in the initial treatment of patients with type 1 Gaucher disease (GD) is described in this issue of Blood by Lukina and colleagues.1 The hope is that this finding will lead to the first efficacious oral therapy for GD.

The discovery of the nature of the enzyme deficiency in GD2 led to the production of an extracted placental-derived enzyme and then recombinant enzyme. The therapeutic application of these products, first reported in 1991, has become the standard of care for GD patients and has resulted in major benefits for large numbers of patients around the world.3 The benefits include improvements in hemoglobin and platelet counts, reduction in size of organs enlarged by infiltration by glucosylceramide-laden macrophages (liver and spleen), and improvement in bone marrow infiltration and secondary skeletal effects. Very few patients are intolerant of enzyme replacement therapy but the need for intravenous infusions every 2 weeks for life is both daunting and logistically difficult. An alternate approach to reducing the accumulation of ceramide is to interrupt the pathway of synthesis. The first approved molecule using this approach was miglustat (Zavesca), which was shown to have activity in a majority of patients in small studies and has resulted in its marketing for adult patients for whom enzyme replacement is “not an option.” This agent has had only limited application internationally because of concerns about toxicity and efficacy. Results of a maintenance study have been published4 and a further maintenance study has recently been completed, follow-up with results forthcoming.

This report of a multinational phase 2 study in 26 previously untreated patients with type 1 (nonneuronopathic) GD treated with eliglustat, a newer substrate reduction agent, showed that a majority of subjects achieved the composite primary endpoint for efficacy. This was most evident in reduction of liver and spleen size (22 patients of 26 at risk) and an increase in hemoglobin (9 of 10 at risk) and platelet count (16 of 25 at risk). Meaningful and sustained improvements in the recognized biomarkers of disease activity, chitotriosidase and CCL18, were also observed and improvement in bone density Z and T scores in the lumbar spine (but not the femur) occurred. Bone marrow infiltration and areas of infarction were apparently stable except in 1 patient with progressive infarction. This most important complication of GD requires further evaluation as improvement with enzyme replacement has been reported to take years in some patients.5 Unlike miglustat, neither intolerance nor neurologic effects such as tremor or peripheral neuropathy was observed and only mild gastrointestinal events were seen in 3 patients. Two patients treated with eliglustat developed asymptomatic cardiac tachyarrhythmias.

Like all studies of extremely rare conditions, the size of the patient population and the lack of a control arm are significant shortcomings of a trial of therapeutics in extremely rare hematologic conditions, although at least one recent example suggests that randomized trials in some rare disorders may be possible, provided suitable short-term endpoints are identified.6

An oral medication with apparent significant activity in this group of patients with a serious very rare disease would be a welcome addition. Longer-term follow-up in this and other patient populations is required to determine whether the observed effects are sustained and/or bone consequences are improved, and to evaluate the nature and incidence of any long-term toxicities.

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REFERENCES


Comment on Hartmann et al, page 953

**Discovery of Hippo in MCL**

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In this issue of Blood, Hartmann and colleagues report on the results of a high-resolution genomic profiling study in a large series of MCL. Copy number alteration and expression data are amalgamated with clinical outcome. Their data confirm the critical role of the cell-cycle and DNA damage-response pathways to MCL and also identify novel target genes within these. Specifically, Hippo signaling is recognized as a potentially novel pathogenetic pathway.1

![Figure 1. Schematic diagram summarizing the cell-cycle and DNA damage response alterations in MCL, highlighting specific genomic copy number variations. The t(11;14)(q13;q32) translocation results in up-regulation of cyclin D1, an important regulator of the G1 phase of the cell cycle with its catalytic partner cyclin-dependent kinase 4 (CDK4). Overexpression of cyclin D1 maintains retinoblastoma (Rb) in a phosphorylated state leading to its inactivation and release of its suppression on the transcription factor E2F. E2F transactivates numerous S-phase gene promoters (cyclins D, E, A) and thus instigates DNA synthesis. Alterations described by Hartmann et al may act in the following ways. ATR4 binds to CDK2A/p16 causing p16 activation. Loss of CUL4A prevents cell-cycle inhibition through p16. ING1 increases p21 expression by up-regulating the DNA damage-response gene p53. The loss of ING1 enhances cell-cycle progression through the G1/S checkpoint by removing the p21 brake. In MCL, MCPH1 is down-regulated leading to its inactivation and release of its suppression on the transcription factor E2F. E2F overexpression of cyclin D1–positive cases, confirming again that these represent the same pathogenic entity and raising the possibility that genetic profiling could be used as an aid to diagnosis when difficulties exist by providing a robust means of identifying this particular disease subtype.

By incorporating clinical survival with genomic data, this study nicely highlighted those genomic alterations that were most likely to influence the clinical course of the disease. Previous studies have identified key alterations relating to the genes that control cell cycle and response to DNA damage and these are confirmed here (summarized in Figure 1).

Genomic amplification of cyclin-dependent kinase 4 (CDK4), deletion of cyclin-dependent kinase inhibitor 2A/p16 (CDKN2A), and overexpression of BIM1 (a transcriptional repressor of p16) all contribute to increasing the protein drive on cell cycling and proliferation.2 Loss of response to DNA damage through ATM and TP53 mutations further promotes cell cycling. Here Hartmann and colleagues provide good evidence that the regions of common loss are characterized by survival genes, associated with the proliferation signature3 that is critical to MCL pathogenesis. In this way, these data also suggest that subsets of genes encompassed by minor common regions of change impact on patients’ outcome and have prognostic value. MCL is a “spectrum of diseases” with no clear best method for risk stratification besides continuous variables including MCL International Prognostic Index and Ki67. By identifying different molecular subsets this provides new clinically relevant prognostic stratification.

Although the hallmark of mantle cell lymphoma (MCL) is overexpression of cyclin D1 related to the t(11;14) translocation, it is clear that there are a number of biologic factors synergizing in the disease process. Their identification has contributed to the provision of prognostic molecular markers, and such secondary genomic alterations are likely to account for the highly variable clinical behavior of MCL and may permit better risk stratification at diagnosis. Most of the additional abnormalities identified to date perturb the cell-cycle machinery and interfere with the cellular response to DNA damage.2 Our knowledge, however, of the biology of this disease is by no means complete. There have been a number of studies exploring copy number alteration.3,4 This research paper presents the largest dataset to date, using high-resolution techniques to power this study to combine genome-wide copy number alteration with gene expression and clinical data in a cohort of primary MCL cases. Importantly, this permitted identification of new survival–associated genetic alterations affecting prognosis and revealed potential new pathogenetic pathways.

This report confirms the complexity of the secondary genomic imbalances that occur in MCL. The few cases of cyclin D1–negative MCL included were found to carry the same types of abnormalities and complexity as cyclin D1–positive cases, confirming again that these represent the same pathogenic entity and raising the possibility that genetic profiling could be used as an aid to diagnosis when difficulties exist by providing a robust means of identifying this particular disease subtype.

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