Course of the pain crisis (1 or no days of pain prior to evaluation), nor was it beneficial for children who were stratified by the number of hospitalizations in the previous 3 years. The secondary end points of opioid use, health-related quality of life and biomarkers, were also similar between the 2 groups. The authors concluded that magnesium is not effective for VOC in children with SCA.

At first glance, MAGiC may be interpreted as a “negative” trial because magnesium infusions did not improve VOC. Although these results are disappointing, an important result and accomplishment of the MAGiC trial is less readily apparent. In particular, the MAGiC team produced a potential solution for a problem that SCD investigators have struggled with for years—MAGiC made participants appear. Since 2008, >15 multi-institutional clinical trials for SCA were closed prematurely due to low enrollment. Failure to enroll an adequate number of subjects in a clinical trial is costly and may expose participants to risks of toxicity without providing the potential benefits of a successful study. With these challenges in mind, the MAGiC team created a unique partnership between Pediatric Hematologists and Emergency Department Physicians in the Pediatric Emergency Care Applied Research Network. Impressively, in 8 medical centers from December 2010 to December 2013, 807 children were screened for eligibility. Of those eligible, 76% (n = 410) were approached, and 39% (n = 214) of children enrolled. On average, the MAGiC team enrolled 1 patient per site per month and completed their enrollment goals in 2 years, a rate of patient accrual that surpasses most other clinical trials for SCA.

Recent insights into the pathophysiology of SCA and mechanisms of globin gene expression promise innovative new therapies, which must be vetted efficiently and rapidly in a patient population that has historically been difficult to enroll in clinical trials. The legacy of the MAGiC trial may be its development of an improved model for participant identification, screening, and enrollment based on multidisciplinary collaborative interactions between pediatric health care providers. Adoption of this paradigm for future trials should ultimately benefit individuals with sickle cell disease by magically accelerating the identification of effective new therapies.

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Is the open mouth mightier than the needle?

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In this issue of Blood, Bernard et al provide evidence that ibrutinib, the orally administered inhibitor of Bruton tyrosine kinase (BTK), crosses the blood-brain barrier and has activity against mantle cell lymphoma (MCL) in the central nervous system (CNS). Over the last decade, several groups have evaluated the incidence and risk factors for CNS involvement by MCL. Like diffuse large B-cell lymphoma (DLBCL), roughly 5% of patients with MCL will develop CNS disease. Like DLBCL, patients with the most aggressive MCL biology (eg, blastoid histology, high lactate dehydrogenase, and high Ki67) are most likely to experience CNS relapse, as many as 25% in some reports. Like DLBCL, there is limited evidence in MCL that the choice of primary therapy impacts the incidence of CNS relapse. The use of agents with potential activity against CNS lymphoma, including rituximab, high-dose cytaraabine, methotrexate, and autologous stem cell transplantation, was not associated with a reduced risk of CNS involvement in 3 retrospective series, although the dosing of methotrexate may have been suboptimal for CNS penetration, and the use of prophylactic intrathecal therapy was not reported. Finally, like DLBCL, the survival of people that experience CNS progression of MCL is typically poor despite subsequent administration of CNS-directed intravenous or intrathecal therapies (see figure). However, MCL and DLBCL are biologically distinct entities, and there are important differences with respect to CNS involvement. Unlike DLBCL, which tends to relapse in the brain parenchyma within the first 6 months of diagnosis, the average time to progression of MCL in the CNS, often with leptomeningal disease, is typically >1 year from diagnosis and frequently occurs after multiple prior lines of therapy. Unlike DLBCL, regardless of location, MCL is not curable.

Recent reports of oral agents with newly discovered activity against CNS lymphomas

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provide great news for patients. There have been multiple reports, including at least 1 prospective clinical trial, demonstrating the activity of oral lenalidomide for primary CNS lymphoma.\textsuperscript{5,6} Although the report from Bernard et al consists of just 3 patients, the data demonstrate that ibrutinib may have durable clinical benefit in some patients with CNS MCL. That 2 of the 3 patients had a Ki67 of $>60\%$ makes the report even more remarkable, given the suggestion that ibrutinib is less effective in more proliferative tumors.\textsuperscript{8} It raises the question of whether ibrutinib might have a differential effect on tumor cells in the CNS compared with the lymph node microenvironment. It is likely that we will see additional reports of similar activity in the future, but given publication bias toward positive results, it is unlikely that we will gain a true idea of the activity of ibrutinib against CNS MCL outside of a clinical trial like the National Cancer Institute phase 2 trial of immunotherapy plus ibrutinib in primary CNS lymphoma.\textsuperscript{9} Prospective trials will also be required to better define the pharmacokinetics of ibrutinib in the cerebrospinal fluid (CSF), including CNS penetration, as the blood-brain barrier evolves during tumor resolution. Still larger data sets might be required to interpret the pharmacokinetics relative to clinical response. It is worth noting that in the initial phase 1 trial with ibrutinib, doses as low as 1.25 mg/kg achieved serum concentrations that exceeded the ICS50 (and the CSF concentration reported by Bernard et al), whereas 2.5 mg/kg was sufficient to achieve maximal BTK occupancy 4 hours after administration, and the standard 500 mg daily dose of ibrutinib approved for MCL is threefold higher.

The Bernard et al data raise the question of whether we might see new strategies to reduce the occurrence of MCL progression within the CNS among high-risk patients similar to strategies used in DLBCL. It may be more challenging to answer questions about CNS prophylaxis than it is to demonstrate activity of an agent against CNS MCL. The mere concept that front-line therapy might impact CNS progression is challenging to grasp given that CNS progression is frequently a late event. Unfortunately, clinical trials rarely collect data on sites of relapse or outcomes of subsequent therapies, and this information is challenging to collect retrospectively. Moreover, better front-line strategies may paradoxically give the appearance of an increase in the incidence of CNS involvement if more patients live longer. Similarly, because MCL is likely as incurable in the CNS as it is elsewhere, it is possible that different front-line strategies will not actually impact the incidence but rather the timing of CNS progression (still a worthy goal). Reports of overall incidence may be less informative than time-to-event statistics. Finally, because the proportion of patients at highest risk for CNS progression is quite low in most clinical trials, individual studies may have limited power to demonstrate a difference and meta-analyses may be required.

Regardless of the challenges involved in data interpretation, the fact that there are now well-tolerated agents with a hint of activity against CNS MCL is a step forward. Reports such as this one by Bernard et al demonstrate the ongoing importance of clinical observation.

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