The problem is that all of this seemingly coherent and elegant iron trafficking story, including the idea that the L-type calcium channel blocker amlodipine, as well as other calcium channel blockers can modulate cardiac iron trafficking, is derived from in vitro studies in cell culture and from knockout mice. Certainly, serial measurements showing differential rates of loading and unloading during chelation in the liver, endocrine organs, and heart in humans are consistent with the elegant biochemistry worked out in the laboratory. However, some hand waving is required to explain this organ-specific iron trafficking in humans, because mice are not humans. Fernandes et al have shown that the effect of calcium channel blockade amlodipine on cardiac iron loading predicted in animals also resulted in reduced cardiac iron in humans. As the authors point out, more clinical studies need to continue because all calcium channel blockers do not have the same effect in vitro, but at least the “channels” for more progress on both clinical and biochemical fronts are now open.

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● ● ● CLINICAL TRIALS AND OBSERVATIONS

Comment on Chen et al, page 1562

BV for HL: can the responses last?

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In this issue of Blood, Chen et al report the long-term follow up from a cohort of relapsed/refractory (R/R) Hodgkin lymphoma (HL) patients, who received single-agent brentuximab vedotin (BV) in a phase 2 pivotal trial, revealing a 5-year overall survival (OS) and 5-year progression-free survival (PFS) of 41% and 22%, respectively (see figure).1

The original report from this trial demonstrated an overall response rate of 75% and a complete response (CR) rate of 34%, leading to accelerated US Food and Drug Administration (FDA) approval for patients with R/R HL after hematopoietic autologous stem cell transplantation (auto-SCT) or failure of at least 2 prior therapies.2 BV, a novel antibody drug conjugate, has been described as a “game changer” in HL. Is BV living up to the hype? Of the 102 patients enrolled, 13 remain in continuous complete remission >5 years from registration. Of the 13 patients, 9 achieved this result having received only BV, whereas 4 received BV followed by hematopoietic allogeneic SCT (allo-SCT). Although 9% durability for BV alone may not seem like a noteworthy outcome, recall that these are generally young patients who had received 2 prior attempts at curative therapy (frontline therapy and auto-SCT). Given that the median age of the cohort was only 31, any degree of remission durability is meaningful. Long-term follow up also affords an opportunity to examine long-term toxicity. In the original publication on this cohort, 42% of patients experienced peripheral neuropathy (PN), of which 8% was grade 3.2 PN, even grades 1 to 2, is often a source of daily aggravation and frustration for patients. In this updated report, we learn that 88% of patients experienced either resolution (73%) or improvement (14%) in symptoms.

Do these results signify a significant therapeutic advance? Yes. Could similar results have been obtained with already available agents and strategies? Maybe, but patients likely would have endured more toxicity.
and morbidity to get comparable efficacy. Therefore, although the single-agent activity of BV is not a definitive solution for the majority of HL patients, it does provide an attractive option, which can provide a bridge to other therapies such as allo-SCT or the highly promising programmed death-1 (PD-1) and PD ligand-1 pathway inhibitors. What is sorely needed is a biomarker that could prospectively identify which patients are likely to be a long-term responder to single-agent BV. The authors report that the patients with sustained CR tended to be younger, have more extranodal disease, and a shorter interval from diagnosis to BV treatment. These are interesting observations, but given the very small numbers of patients, they are not reliable enough to guide practice.

As with any promising new drug, the real challenge is not in defining the single-agent activity but rather determining how to incorporate it into existing therapies. BV has since gained an additional FDA indication in HL, to be used as a consolidative therapy post-auto-SCT in high-risk patients. The AETHERA trial demonstrated that BV post-auto-SCT significantly improves PFS compared with placebo, although no impact on OS has been observed to date. Appropriately, BV is working its way up the treatment paradigm, being tested earlier and earlier in the disease course. For example, it has been used sequentially with ifosfamide, carboplatin, and etoposide chemotherapy as a bridge to autologous stem-cell transplantation. Frontline phase 2 studies in early stage sequentially with ifosfamide, carboplatin, and etoposide chemotherapy as a bridge to autologous stem-cell transplantation in patients with Hodgkin’s lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2015;385(9980):1853-1862.


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Comment on Souilhol et al page 1567

Turning it down a Notch

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In this issue of Blood, Souilhol et al pinpoint the requirement for Notch signaling to precisely defined stages in hematopoietic stem cell (HSC) emergence and implicate both Notch1 and Notch2 in this process.

Definitive HSCs have been used in transplantation therapies for blood-related disorders for decades. The inability to expand them in vitro, or generate bona fide HSCs from pluripotent stem cells, has sparked a great interest in understanding how HSCs are generated de novo during embryonic development. A mechanistic understanding of this holds promise for the development of robust in vitro culture methods to generate HSCs for research and ultimately for therapeutic purposes such as autologous gene correction for single gene hematologic disorders. During embryonic development, HSCs are generated autonomously in the aorta-gonad-mesonephros region (AGM), where they emerge in clusters of hematopoietic cells that bud from the hemogenic endothelium in the ventral wall of the dorsal aorta. The emergence of HSCs is controlled by several signaling pathways, including Notch. Notch signaling is required for early hematopoietic specification of the HSC lineage. Later on, its activity is downregulated in the aortic hematopoietic clusters, but the precise cellular stage at which it is active remained to be established (see Butko et al for a recent review).

Medvinsky and coworkers recently identified the direct cellular precursors to the definitive HSC, the pre-HSC type I and II. These cells express the hematopoietic marker CD41 and lack in vitro endothelial potential, indicating that they have already diverged from the hemogenic endothelium. The group showed that on ex vivo culture, pre-HSC type I mature via pre-HSC type II into definitive, transplantable HSCs. Building on from this, Souilhol et al set out to address where in the HSC lineage Notch signaling is active and required, using several complementary in vitro and in vivo approaches. Notch activity was assessed through ex vivo culture and transplantation of Hes1–green fluorescent protein.
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Brad S. Kahl