Preclinical pain research has yielded few translational successes over the past several decades, perhaps because of overreliance on rodent models.[2,3] Many groups, including our own, now routinely incorporate, or exclusively study, novel pain targets in human tissue to increase target translatability. Particular focus has been placed on targets in dorsal root ganglia afferents, the first neurons through which internal and external sensory information is transduced and transmitted to the central nervous system. Over the past decade, accessibility of healthy human nervous system tissue for these types of studies has dramatically increased through academic partnerships with organ donor procurement organizations. However, tissue from select patient groups, including those with SCD, will likely never be attainable through these avenues. Knowing this, the authors of this article instead chose to derive sensory neurons from patient and healthy control iPSCs using well-defined methods.[4]

The results reported by Allison and colleagues are the best attempt, to date, to bridge the gap between sickle cell pain mechanisms originally characterized in transgenic mouse models and the pain mechanisms that are actually at play in patients. Notable similarities between patient iPSC sensory neurons and SCD mouse sensory neurons include hyperexcitability as measured by increasing action potential firing upon sustained depolarization and endothelin-1-induced sensitization.[5] Exposure to plasma that was collected from patients during an acute pain event further sensitized patient iPSC sensory neurons; although not examined in this study, exposure to pain-associated plasma may also induce direct activity in patient iPSC sensory neurons like that observed in SCD mouse afferents during hypoxia-reoxygenation.[6] In the current set of experiments, the authors did not identify a specific target that, when blocked, could prevent plasma-associated neuron sensitization. This should be the focus of future investigation, given the potential therapeutic relevance of that outcome.

Notable differences were also observed between patient iPSC and SCD mouse sensory neurons. For example, no spontaneous activity was reported in patient iPSC neurons; this has been reported in SCD mouse dorsal root ganglia neurons by more than 1 preclinical laboratory.[5,7] Capsaicin sensitization, both in naive cells and following CCL2 incubation, was also notably absent from patient iPSC sensory neurons, despite being reported in SCD mouse sensory neurons.[8] These results, and future studies that reveal similar discrepancies between rodent and human, may suggest deprioritization of targets originally characterized in SCD mouse models. However, combined use of both live SCD mice and patient-derived iPSC sensory neurons may be the most successful path forward given that the latter are not, in fact, a perfect copy of patient dorsal root ganglia neurons. Patient iPSC neurons lack many of the functional connections that exist in vivo; the cells themselves are notably smaller than real human dorsal root ganglia neurons and, despite numerous similarities, still have quite different transcriptomes[9]; and perhaps most notably, iPSC-derived neurons are exposed to circulating factors for significantly less time than dorsal root ganglia neurons from both transgenic mice and patients. Altogether, this study is a landmark for the field because it moves our understanding of sickle cell pain mechanisms forward and because it shows a path for how mouse models, human iPSC sensory neurons, and human neurons from organ donors can be used in combination to zero in on pain mechanisms in SCD that will have the biggest potential impact on pain outcomes in patients in need.

Conflict-of-interest disclosure: K.E.S. and T.J.P. declare no competing financial interests. ■

REFERENCES

1. Allison RL, Welby E, Ehlers V, et al. Sickle cell disease iPSC-derived sensory neurons exhibit increased excitability and sensitization to patient plasma. *Blood*. 2024;143(20):2037-2052.
2. Sadler KE, Mogil JS, Stucky CL. Innovations and advances in modelling and measuring pain in animals. *Nat Rev Neurosci*. 2022;23(2):70-85.
3. Renthal W, Chamessian A, Curatolo M, et al. Human cells and networks of pain: transforming pain target identification and therapeutic development. *Neuron*. 2021;109(9):1426-1429.
4. Chambers SM, Qi Y, Mica Y, et al. Combined small-molecule inhibition accelerates developmental timing and converts human pluripotent stem cells into nociceptors. *Nat Biotechnol*. 2012;30(7):715-720.
5. Lutz BM, Wu S, Gu X, et al. Endothelin type A receptors mediate pain in a mouse model of sickle cell disease. *Haematologica*. 2018;103(7):1124-1135.
6. Sadler KE, Langer SN, Menzel AD, et al. Gabapentin alleviates chronic spontaneous pain and acute hypoxia-related pain in a mouse model of sickle cell disease. *Br J Haematol*. 2019;187(2):246-260.
7. Uhelski ML, Gupta K, Simone DA. Sensitization of C-fiber nociceptors in mice with sickle cell disease is decreased by local inhibition of anandamide hydrolysis. *Pain*. 2017;158(9):1711-1722.
8. Sadler KE, Zappia KJ, O'Hara CL, et al. Chemokine (c-c motif) receptor 2 mediates mechanical and cold hypersensitivity in sickle cell disease mice. *Pain*. 2018;159(8):1652-1663.
9. Tavares-Ferreira D, Shiers S, Ray PR, et al. Spatial transcriptomics of dorsal root ganglia identifies molecular signatures of human nociceptors. *Sci Transl Med*. 2022;14(632):eabj8186.

https://doi.org/10.1182/blood.2024024328

LYMPHOID NEOPLASIA

Comment on Hayashi et al, page 2053

MRD: also for T-lymphoblastic lymphoma

Josep-María Ribera | Josep Carreras Research Institute

In this issue of *Blood*, Hayashi et al[1] assessed the correlation of the level of measurable residual disease (MRD) at the end of induction (EOI) with event-free survival (EFS) in a subset of children and young adults (aged 1-30 years) with T-cell lymphoblastic lymphoma (T-LL, n = 86) treated in a phase 3 trial by the Children's Oncology Group (COG). The group showed that patients with MRD < 0.1% (n = 75) at EOI had a better 4-year EFS vs those with MRD >

0.1% (n = 11). The authors suggest incorporating EOI MRD as an essential tool for prognostication of patients with T-LL.

T-LL is mostly seen in adolescents and young adults, has a male predominance, and usually presents with advanced stage III to IV disease; 90% of patients have a mediastinal mass, sometimes with concomitant pleural and pericardial effusions. Central nervous system (CNS) involvement is seen in 5% to 10% of cases, and diffuse adenopathy or other organs are involved in 70% of cases. Clinically, T-LL and T-cell acute lymphoblastic lymphoma (T-ALL) are separated by an arbitrary cut point of 25% bone marrow infiltration, although there are differences between these 2 diseases at a genetic level.[2,3] T-LL shows a prevalence of 70% of the thymic subtype. Treatment should be based on ALL regimens.[4] In adults, complete remission (CR) is achieved in 70% to 90% of cases in most studies, and the EFS probability is 60% to 70% at 5 years.[5] Better results are observed in children, with EFS reaching 80% to 90%.[6] In view of these results, hematopoietic stem cell transplantation is reserved for patients in second CR or refractory disease.

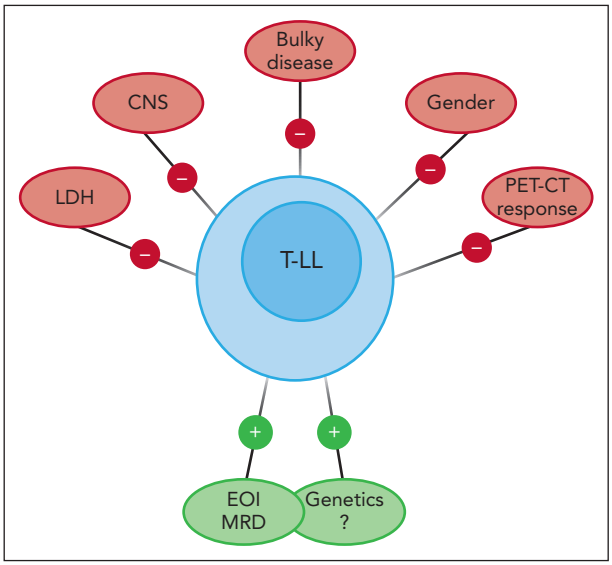
There are no universally accepted adverse prognostic factors for T-LL. They differ across trials, such as increased lactate dehydrogenase, CNS involvement, and genetic classification, among other factors.[4] Traditional variables such as race, age, sex, stage, bulky disease, or radiologic response to therapy have failed to correlate with EFS in children and adolescents (see figure). The prognostic value of positron emission tomography–computed tomography (PET-CT) imaging in T-LL remains unclear.[7] As MRD is prognostic for most hematologic malignancies, it seems logical to look for the prognostic value of MRD in the bone marrow at a relevant time point such as EOI. Hayashi et al demonstrated that MRD at EOI, assessed with flow cytometry with a validated sensitivity of 0.01%, is an independent risk factor for EFS regardless of the treatment arm in the AALL1231 randomized trial (COG study of modified augmented Berlin-Frankfurt-Münster backbone vs the same schedule with the addition of bortezomib during induction and delayed intensification).

Identification of the prognostic value of MRD represents a step forward in T-LL given the lack of consistently proven prognostic factors available to date. As the sample size in the present study was limited, the authors recognized that incorporation of MRD at the EOI in large clinical trials will be needed to definitively establish its future value in risk stratification. However, it seems logical to assume that this will be the case, as MRD is predictive in T- and B-cell precursor ALL.

Some questions arise from the results presented. (1) Is bone marrow involvement detectable by flow cytometry at diagnosis in all patients with T-LL? (2) Is the EOI MRD level correlated with the genetic or genomic abnormalities of T-LL,[8,9] or can it be considered independently for prognosis assessment? (3) Could the cutoff level of 0.01% at EOI be more useful for prognosis than 0.1%? (This question was not fully addressed in the study by Hayashi et al probably due to the small sample size.) (4) Is the sensitivity level of 0.01% achieved by conventional flow cytometry sufficient? (5) Is EOI the only time point useful for prognostication, or do we need MRD assessment after consolidation as occurs in ALL? (6) Does the EOI MRD level correlate with the clearance of extramedullary disease assessed by PET-CT scan? And (7) does MRD have the same prognostic value after treatment for relapse?

The study by Hayashi et al has obvious clinical relevance. As T-LL and T-ALL are considered within the spectrum of the same disease from a therapeutic point of view, it seems logical to address the same questions of MRD as those used for T-ALL. Given the low frequency of T-LL, well-designed multicenter trials are necessary to achieve this objective.

Conflict-of-interest disclosure: J.-M.R. declares no competing financial interests. ■



Favorable and unfavorable prognostic factors in children and adolescents with T-LL.

REFERENCES

1. Hayashi RJ, Hermiston ML, Wood BL, et al. MRD at the end of induction and EFS in T-cell lymphoblastic lymphoma: Children's Oncology Group trial AALL1231. *Blood*. 2024;143(20):2053-2058.
2. Bontoux C, Simonin M, Garnier N, et al. Oncogenetic landscape of T-cell lymphoblastic lymphomas compared to T-cell acute lymphoblastic leukemia. *Mod Pathol*. 2022;35(9):1227-1235.
3. Raetz EA, Perkins SL, Bhojwani D, et al. Gene expression profiling reveals intrinsic differences between T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma. *Pediatr Blood Cancer*. 2006;47(2):130-140.
4. Si Lim SJ, Ford JB, Hermiston ML. How I treat newly diagnosed and refractory Tcell acute lymphoblastic lymphoma in children and young adults. *Blood*. 2023;141(25):3019-3030.
5. Lepretre S, Touzart A, Vermeulin T, et al. Pediatric-like acute lymphoblastic leukemia therapy in adults with lymphoblastic lymphoma: the GRAALL-LYSA LL03 study. *J Clin Oncol*. 2016;34(6):572-580.
6. Hayashi RJ, Winter SS, Dunsmore KP, et al. Successful outcomes of newly diagnosed T lymphoblastic lymphoma: results from Children's Oncology Group AALL0434. *J Clin Oncol*. 2020;38(26):3062-3070.

7. Becker S, Vermeulin T, Cottereau AS, Boissel N, Vera P, Lepretre S. Predictive value of 18)F-FDG PET/CT in adults with T-cell lymphoblastic lymphoma: post hoc analysis of results from the GRAALL-LYSA LLO3 trial. *Eur J Nucl Med Mol Imaging*. 2017;44(12):2034-2041.

8. Khanam T, Sandmann S, Seggewiss J, et al. Integrative genomic analysis of pediatric Tcell lymphoblastic lymphoma reveals candidates of clinical significance. *Blood*. 2021;137(17):2347-2359.

9. Callens C, Baleydier F, Lengline E, et al. Clinical impact of NOTCH1 and/or FBXW7 mutations, FLASH deletion, and TCR status in pediatric T-cell lymphoblastic lymphoma. *J Clin Oncol*. 2012;30(16):1966-1973.

https://doi.org/10.1182/blood.2024024344

PLATELETS AND THROMBOPOIESIS

Comment on Kogler et al, page 2073

Platelets: let's chill until more data arrive

Kristin M. Reddoch-Cardenas and Michael A. Meledeo | US Army Institute of Surgical Research

In this issue of *Blood*, Kogler et al present novel findings on the in vivo function of 14-day cold-stored platelets (CSPs) in plasma.[1] There has been a resurgence in CSP use for therapeutic transfusion over the past decade. Unlike room temperature–stored platelets (RSPs), which have increased transfusion-transmitted infection (TTI) risk, require constant agitation, and are short-lived (5-7 days), CSPs carry a reduced TTI risk, require no agitation, and offer extended shelf life (currently 14 days with potential for 21 days). US Food and Drug Administration (FDA) guidance on platelets[2] (June 2023) allows CSPs for treatment of active bleeding "when conventional platelets are not available or their use is not practical." Conversely, recent FDA guidance (December 2020) requiring enhanced testing or pathogen reduction of RSP underscores their TTI risks.[2]

The transfusion model evaluated by Kogler et al consisted of endogenous platelet cyclooxygenase-1 inhibition by acetylsalicylic acid (ASA) ingestion with evaluation of posttransfusion performance of CSPs determined at 1, 4, and 24 hours. Interestingly, and in contrast with 7-day RSPs, 14-day CSPs were unable to restore platelet function at any time point. The authors acknowledge that this contradicts prior CSP studies in ASA-treated volunteers, although those were performed with whole blood–derived platelets rather than apheresis products. Because of, at least in part, cold-induced receptor clustering and alterations to glycoprotein expression,[3] CSPs are cleared rapidly from circulation in noninjured, healthy subjects on transfusion, a trait demonstrated by Murphy and Gardner[4] in 1969, which ultimately resulted in abandonment of their use for decades. Several laboratories, including our own,[5] have demonstrated enhanced hemostatic function in CSPs by several metrics; Kogler et al report that CSPs are more procoagulant than RSPs, primarily through the enhanced thrombin generation capacity of CSPs. It is plausible that rapid clearance of hemostatically functional CSPs leaves behind phosphatidylserine-expressing platelets whose primary hemostatic competency is to generate thrombin, akin to those described by Vulliamy et al.[6] Indeed, Kogler et al demonstrated a declining corrected count increment over time for CSPs, consistent with prior work showing more rapid clearance than RSPs.

Despite the lack of a nucleus, platelets are complex cells that participate in a host of functions, including hemostasis, thrombosis, wound healing, and immune responses to injury. Aggregometry (typically by light transmission or electrical impedance methods) has historically been considered the "gold standard" of platelet functional evaluations, but Kogler et al acknowledge the limitations of this in vitro method: it is time-consuming, requires large sample volumes, and does not adequately model the complex interactions in which platelets engage. Assays, such as aggregometry and viscoelastometry, thus far, have been poor predictors of posttransfusion platelet clinical function. Although Kogler et al present an innovative strategy to predict aggregation responses in vivo, ultimately their conclusions are based on thrombin generation and aggregation assays as surrogate functional markers, relying on ex vivo benchtop testing rather than patient outcomes. They acknowledge the limitation of using healthy recipients who do not demonstrate a clinical need for platelet transfusion.

Although novel approaches to understanding functional mechanisms will undoubtedly reveal more insights into the biology/pathophysiology of platelets, when it comes to patient care, the research community must answer 2 primary questions for a transfusion product: (1) does it do more good than harm, and (2) can it be efficiently supplied? CSPs already help fulfill the latter criterion through their inherently improved bacterial safety and shelf life, and clinical trials in bleeding patients should answer the former. Although Kogler et al present the first posttransfusion comparison of CSPs and RSPs stored in plasma to the end of their shelf lives, the authors note that their work should be evaluated with caution until clinical trial data are generated. Fortunately, randomized clinical trials are underway and being reported. Strandenes et al[7] reported hemostatic efficacy of (up to) 14-day CSPs, as measured by chest drain output, in a pilot trial involving complex cardiothoracic patients. The ongoing Chilled Platelet Study (CHIPS; NCT04834414), a phase 3, randomized, multicenter, international study evaluating blood product use, chest tube output, and additional functional outcome measures posttransfusion of platelets in adult and pediatric cardiac surgery patients, should be even more informative, as transfused platelet units are derived from a variety of collection platforms and storage temperatures/durations (up to 21 days), with or without