the US Food and Drug Administration approved enasidenib for the treatment of relapsed and refractory IDH2 mutant AML in 2017. In this issue of *Blood*, de Botton and colleagues report the results of the logical successor study, a randomized phase 3 study of enasidenib vs "conventional care regimens" in patients 60-years of age or older with IDH2-mutant relapsed and refractory AML.[6] In this study, patients with relapsed or refractory AML after 2-3 lines of prior treatment were randomized in an open-label fashion to receive enasidenib or 1 of 4 conventional care regimens: intermediate dose cytarabine, azacitidine, low dose cytarabine or best supportive care alone. The results are unexpected. Despite improvements in the overall response rate, time to treatment failure, and a modest improvement in event free survival, all favoring enasidenib, the overall survival between enasidenib and the conventional care arm was equivalent. How is this possible? How is it that a differentiation agent that avoids myelosuppression fails to improve survival over myelosuppressive therapy or no treatment at all? Perhaps more importantly, should we interpret these results to mean that patients with relapsed and refractory IDH2 mutant AML should not get enasidenib?

The answer to this conundrum can be found in a detailed look at the CONSORT diagram in the study results. 12.4% of the patients randomly assigned to the conventional care arm dropped out of the study before receiving their allotted treatment compared with only 1 patient randomly assigned to enasidenib. Similarly, 34 patients allocated to the conventional care regimen were discontinued from treatment by their physician because of "no treatment benefit," something that did not happen to any patient randomly assigned to enasidenib. 24 patients self-discontinued treatment in the conventional care regimen compared with only 10 patients in the enasidenib arm. In total nearly 50% of patients allocated to the conventional care arm did not actually receive a full course of conventional care.

It is easy then, to understand what may have happened. Because of the open-label nature of the study, patients randomly assigned to a conventional care regimen chose to receive other therapy—perhaps even enasidenib itself—rather than their allotted treatment. Because of this, the overall survival results are hopelessly confounded and should not be used to guide clinical practice toward or away from enasidenib.

One final question that needs to be answered is the relevance of the regimens included in conventional care in 2022. Despite a lack of randomized data, the totality of the clinical data suggests that patients with *IDH*-mutant AML may be particularly sensitive to the combination of azacitidine and the BCL2 inhibitor venetoclax, even in the relapsed and refractory setting.[7,8] A more useful and practical clinical study would involve randomly assigning patients with *IDH2*-mutant relapsed and refractory AML to enasidenib or azacitidine-venetoclax in a placebo controlled manner, and then assessing for both event-free and overall survival.

Donald ultimately enrolled in the clinical study of enasidenib back in 2014. His leukemia cutis and marrow both cleared up, and he remains in CR while receiving enasidenib in 2022. The promise of enasidenib remains alive.

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CLINICAL TRIALS AND OBSERVATIONS

Comment on Dampier et al, page 168

Ups and downs in the treatment of sickle cell disease

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Despite promising early results, in this issue of *Blood*, Dampier et al[1] report the negative results of rivipansel, a predominantly E-selectin antagonist, in treating hospitalized vaso-occlusive crisis (VOC) in patients with sickle cell disease (SCD). Although these results are disappointing for patients and physicians, important lessons can nevertheless be learned.

SCD is a devastating disease with a huge global burden, affecting more than 100 000 patients in the United States as well as in Europe and millions in low-income countries. Its pathophysiology has emerged as an extremely complex one, involving not only hemoglobin polymerization as the primum movens but also a cascade of interrelated events including hemolysis; activation and adhesion of neutrophils, platelets, and endothelial cells; abnormal coagulation; sterile inflammation; vascular tone impairment; and nitric oxide functional deficit, among other downstream biological consequences.[2] Hydroxyurea, the main drug for the prevention of SCD complications, acts on almost all of these interlocking pieces, starting with antipolymerization effect through the reactivation of fetal hemoglobin, and its use has dramatically improved the prognosis of the disease in treated patients.[3] Importantly, drugs in SCD, including hydroxyurea, have demonstrated benefits in reducing the incidence of related complications but not one single drug is yet available for treating acute VOC, which is the hallmark of SCD and its most frequent painful complication. Consequently, treatment of VOC still relies on symptomatic relief (of pain, inflammation, and anemia, notably), but none can effectively stop the process once it is triggered or accelerate resolution. New drugs that can effectively act on acute vaso-occlusion and/or synergistically address important facets of the pathophysiology of SCD are still urgently needed.

Among recently developed drugs in SCD, those that reduce the abnormal cell-cell interaction and particularly the adhesion of sickled erythrocytes and leukocytes on activated endothelial cells via selectin blockade were designed with the hope of interfering with the process of vaso-occlusion.[4] Recently, crizanlizumab, an anti–P-selectin monoclonal antibody indeed showed effectiveness in reducing vaso-occlusive events in a phase 3 study.[5] Based on promising early results of rivipansel in a phase 2 study,[6] Dampier et al conducted a large, well-designed phase 3 clinical trial that compared the efficacy and safety of rivipansel with placebo administered intravenously in 345 randomized patients including 141 children ≥6 years of age, admitted in hospital for VOC requiring IV opioid analgesics. Results showed no significant benefit on a clinically relevant primary end point, namely the median time for readiness to discharge (ie, only oral pain medication required, acute complications of VOC resolved to the extent that they could be managed as an outpatient, IV hydration discontinued, IV antibiotics discontinued, and blood transfusions no longer required). However, in a post hoc analysis, the authors explored the timing of rivipansel administration after pain onset and suggested that the administration of the drug within 26.4 hours of VOC onset (earliest quartile) may be an important factor for reducing time for readiness to discharge, as well as time to discharge and time to discontinuation of IV opioids.

Time to treatment in general and analgesia in particular have long been recognized as central in the management of VOCs in patients with SCD.[7] Likewise, duration of pain experienced at home before arriving for hospital-based management is an important factor in treatment efficacy. Patient-reported time of vaso-occlusive pain onset was a critical item captured in the study. Although it is a challenging parameter to collect given the subjective nature of pain, the possible progressive beginning, its multifactorial etiology, the notorious variability among subjects, the recall bias and subsequent arbitrary imputation, and individual differences in perception of pain onset, it is now clear that patient-reported outcomes are crucial to collect.[8] Specifically for the vaso-occlusive process, it is likely that early intervention is required to intervene before the inflammatory storm subsequent to ischemia-reperfusion injury causes pain, particularly if the threshold for pain is low, as is the case in many patients with a history of recurrent pain. In fact, the authors point to a narrow time window for early administration of agents that target adhesion processes and suggest home-initiated therapy for best efficacy.

A series of disappointing results from well-conducted trials targeting better resolution of VOC has been published in recent years. Drugs such as poloxamer or sevuparin have failed to demonstrate efficacy.[9,10] Rivipansel will unfortunately be added to this list, and drugs for treating SCD can still be counted on one hand.

SCD is a tremendously challenging disease, including the design of clinical trials. Patient recruitment is difficult in high-income countries where most clinical trials are funded, not only because SCD is a rare disease and the pool of patients is small but also because of poor accrual. End points for efficacy are challenging and need to be refined with composite measures of the response of crisis to treatment, including patient-reported outcomes. Notwithstanding, there has never been such a large number of curative or disease-modifying drugs in the pipeline. Focus on and funding of SCD treatment are growing. Awareness for helping patients feel more engaged in clinical research is also increasing (https://www.hematology.org/about/apps-and-podcasts/scd-podcast-sign-up-form), and advocacy groups are becoming powerful worldwide. Until an affordable curative treatment is made available, there is still a long road ahead before we can offer a tailored and targeted multidrug home-based therapy to patients, but, finally, there is hope of such a therapy being available in the upcoming years.

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LYMPHOID NEOPLASIA

Comment on Gluud et al, page 180

TOXic T-cell cytokines wreak havoc in CTCL skin

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Mycosis fungoides (MF) and Sézary syndrome (SS) are the most common forms of cutaneous T-cell lymphoma (CTCL).[1] Despite being malignancies, the clinical picture of CTCL is characterized by erythematous, eczematous, and papulosquamous skin changes reminiscent of inflammatory skin diseases, such as atopic dermatitis and psoriasis.[2] Indeed, lesional skin of MF and SS is often strongly pruritic and shares histological, molecular, and microbial features with lesional skin of inflammatory skin disease. How malignant CTCL T cells cause such profound inflammatory changes in the skin has been a long-standing question in the field. Although the T helper type 2 (T_H2)–skewed phenotype of clonal T cells has long been suspected to be responsible,[3] mechanistic insight was lacking. In this issue of *Blood*, Gluud et al provide evidence that malignant T cells in CTCL secrete the cytokines interleukin-13 (IL-13), IL-22, and oncostatin M (OSM) to induce JAK-STAT signaling in surrounding keratinocytes, downregulate filaggrin expression, and impair skin barrier function (see figure).[4] Blocking these cytokines or inhibiting downstream JAK-STAT signaling restored these epidermal changes in human skin models. These findings provide formal proof that T-cell–derived cytokines are key mediators of the cutaneous manifestations of CTCL and provide a mechanistic rationale for cytokine and/or JAK targeting in MF and SS.

To study skin barrier integrity in CTCL skin lesions, Gluud et al first determined the protein expression of filaggrin, a key structural protein of the epidermis, and measured transepidermal water loss, a proxy for skin barrier function. Strikingly, filaggrin expression was markedly reduced in the immediate vicinity of malignant Thymocyte selection associated high mobility group box (TOX^+) T cells infiltrating the epidermis of patients with CTCL, which correlated with increased skin barrier permeability. This suggested that malignant T cells might be secreting factors that impacted barrier function, either directly or via an inflammatory micromilieu. This hypothesis was further supported by the STAT3 activation seen in keratinocytes surrounding the malignant T cells. STAT3 signals downstream of several proinflammatory cytokine receptors, thus implying a mechanism involving T-cell–derived cytokines. By studying the secretome of CTCL cell lines and by analyzing an integrated set of single-cell RNA sequencing data, the authors honed in on the cytokines IL-13, IL-22, and OSM as the prime suspects causing STAT3 activation and downregulation of filaggrin expression. Indeed, interference with signaling of these cytokines, by either blocking antibodies or inhibiting the receptor signaling cascade, restored filaggrin expression in in vitro models of human skin. The results indicated that the combination of IL-13, IL-22, and OSM, rather than one single cytokine, was responsible for the changes seen in CTCL skin. Therefore, the authors studied the effect of the JAK1/3 inhibitor tofacitinib, which blocks signaling of all of these cytokines and is widely used in clinical practice to treat inflammatory diseases, on the barrier defects induced by tumor cell–derived cytokines. As expected, tofacitinib restored filaggrin expression and epidermal hyperproliferation in reconstructed human epidermis and in MF skin ex vivo (see figure). Taken together, Gluud et al describe for the first time a cytokine-mediated cross talk between malignant T cells and surrounding keratinocytes that causes defects in the skin barrier of patients with CTCL that is, in principle, amendable by JAK inhibition.

The findings by Gluud et al not only help explain some of the clinical phenomena of CTCL but also raise intriguing questions regarding future therapies. First, they lend further support to the notion that cytokines from malignant T cells are both necessary and sufficient to drive the clinical picture of CTCL.[2] This is a direct parallel to inflammatory skin diseases such as atopic dermatitis, where blocking T-cell–derived cytokines with monoclonal antibodies leads to dramatic improvements of disease. Such cytokine-blocking therapies could be repurposed to treat CTCL. Indeed, the anti–IL-4/IL-13 antibody dupilumab has already been used in patients with CTCL, albeit with controversial results. Both progression of CTCL and rapid control of itch and reversal of T_H2 bias in the skin have been reported.[5,6] Regardless, the article by Gluud et al should spur further research to better understand how cytokine blockade can be leveraged to the benefit of patients with CTCL. Second, the data presented by Gluud et al help explain the abnormal skin microbiome and the high incidence of infections in CTCL. Skin dysbiosis, enabled by skin barrier defects, is a known contributor to skin inflammation, clinical burden, and infectious complications in CTCL.[7] Given that infection is arguably the most common cause of death in CTCL,