*Comment on Kreitman et al, page 996*

# Two-inhibitor salvage therapy for hairy cell leukemia

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**In this issue of *Blood*, Kreitman and colleagues[1] report the results of treatment with dabrafenib plus trametinib in a cohort of patients with relapsed/refractory *BRAF V600E* mutation–positive hairy cell leukemia. This cohort was from a multicenter, open-label, nonrandomized phase 2 basket study of dabrafenib plus trametinib in patients with *BRAF V600E* mutation–positive rare cancers. The patients registered to this trial had been extensively pretreated with standard agents used for hairy cell leukemia. All patients had been treated with purine analogs (either pentostatin or cladribine) and had relapsed or progressed. Most patients underwent at least 2 prior regimens. Prior treatment regimens included multiple agents. For example, 63% of patients had received rituximab, and 20% had received moxetumomab. In this extensively pretreated patient group, the overall response to dabrafenib plus trametinib was 89.1% with 65.5% achieving complete remission. Patients were continued on therapy until unacceptable toxicity, disease progression, or death occurred.**

Of the 55 patients in the treatment group, 49 patients had a confirmed response with progression-free survival and overall survival estimated to be 94.4% and 94.5%, respectively, at 24 months. All patients experienced adverse events with 63.6% experiencing grade 3 or greater events. However, adverse events were manageable through treatment interruption, dose modification, and concomitant medications. With the planned long-term treatment, there were patients who discontinued treatment (22%). In addition, there were patients who developed secondary malignancies. Whether these secondary malignancies were related to the increased risk for malignancy in these patients with hairy cell leukemia or to prolonged treatment with dabrafenib and trametinib requires further consideration. In addition to the aforementioned factors, they had been treated with numerous agents before receiving therapy on this trial.

Tremendous progress in the treatment of hairy cell leukemia over the past 3 decades has resulted in many patients living a nearly normal life span. However, many of these patients relapse and require several additional therapeutic attempts to recapture a remission. Both pentostatin and cladribine have changed the natural history of this disease, but relapse after treatment has prompted continued research to improve the quality of the remissions. The addition of rituximab (Rituxan) to either cladribine or pentostatin at relapse has increased the response rate and duration in these patients after relapse. In fact, investigators have incorporated rituximab into the initial therapeutic regimen in an effort to achieve a longer initial remission.[2] Many investigators incorporate rituximab with a purine analog for patients requiring retreatment after relapse.[3]

Since the discovery of the importance of the gene *BRAF V600E* in the pathogenesis of hairy cell leukemia, inhibition of this target has resulted in induction of remission in many patients with classic hairy cell leukemia.[4,5] Inhibitors of *BRAF V600E* have provided impressive responses in patients with hairy cell leukemia. Addition of rituximab to the *BRAF* inhibitor, vemurafenib, has resulted in durable responses in hairy cell leukemia.[6] Likewise, dabrafenib in combination with the MEK (MAPK/ERK kinase) inhibitor (trametinib) is now used to treat patients with the *BRAF V600E* mutation. This report by Kreitman and colleagues adds the combination of dabrafenib and trametinib to the list of effective inhibitors in patients with relapsed and refractory hairy cell leukemia.

Although cladribine remains the most frequently used agent to induce remission in hairy cell leukemia, it may increase the risk of complications in patients with uncontrolled infection. The treatment of patients with hairy cell leukemia with uncontrolled infection and pancytopenia is particularly challenging. Several reported approaches have included initial treatment with vemurafenib.[7] Recently, patients with classic hairy cell leukemia and the *BRAF V600E* mutation, complicated by active infection, have been successfully treated with a *BRAF V600E* inhibitor with or without rituximab. However, the onslaught of the COVID-19 pandemic has further complicated the use of standard induction therapy with cladribine and rituximab. There is concern that the immunosuppression resulting from the combination of a purine analog and the anti-CD20 monoclonal antibody (rituximab) will markedly suppress the immune system for months, thus increasing the danger to those who become infected with the COVID-19 virus and significantly dampen their response to vaccination.[8]

Consequently, the combination of a *BRAF V600E* inhibitor (dabrafenib) with an inhibitor of downstream *MEK* (trametinib) to induce remission in patients with classic hairy cell leukemia is of interest. Vemurafenib alone is effective in inducing remission in relapsed hairy cell leukemia, but the duration of response to this agent alone is often time limited. Although the addition of rituximab to vemurafenib increases the response in relapsed/refractory hairy cell leukemia, this combination has the potential to increase the risks of immunosuppression and susceptibility to COVID-19. Therefore, strategies incorporating dabrafenib with trametinib are especially appealing as a potential salvage regimen in this disease. The article by Kreitman and colleagues provides a promising therapeutic regimen for

patients with classic hairy cell leukemia who have relapsed and require therapy.

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**GENE THERAPY**

*Comment on Wong et al, page 1007*

# Towards improved yet regulated gene therapy for X-CGD

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**In this issue of *Blood*, Wong et al[1] exploit bioinformatic tools to design and test a minimal (core) promoter region to produce sufficient physiological expression of the *CYBB* gene, which is defective in patients affected by X-linked chronic granulomatous disease (X-CGD). X-CGD is the most common form of CGD in males. CGD is an inborn error of immunity caused by a defective reduced NAD phosphate (NADPH) complex, which is a key component of innate immune defense against bacterial and fungal pathogens.[2] The gp91$^{phox}$ protein encoded by the *CYBB* gene is required for the production of reactive oxidase species and is expressed predominantly in myeloid and B-cell lineages but not in primitive hematopoietic stem and progenitor cells (HSPC).[2]**

Allogeneic transplantation is a curative treatment that may be performed in patients with X-CGD with a well-matched donor. Despite the improved outcomes achieved in the past decade,[3] allogeneic transplantation still carries a significant risk of complications. Autologous HSPC gene therapy (GT) is a promising alternative therapy. Several clinical trials have explored GT for X-CGD using integrating vectors, with more than 25 patients treated to date.[4] The first studies based on the use of γ retroviral vectors were hampered by a high incidence of insertional mutagenesis as well as gp91$^{phox}$ inactivation due to methylation of the viral vector promoter.[2] This suggested that the proper regulation of the *CYBB* gene is critical for safety and success of HSPC GTs, fueling the development of myeloid-restricted gp91$^{phox}$ expression[5] as well as of combined transcriptional and post-transcriptional regulation strategies designed to avoid HSPC ectopic expression.[6] More recently, clinical trials based on lentiviral vectors using a chimeric myeloid promoter showed initial evidence of restored NADPH activity and clinical efficacy.[7] However, transgene expression did not reach physiological levels, and the proportion of oxidase-positive cells was variable (1% to 63% at last follow-up).[7] These results, together with recent evidence suggesting that chronic inflammation in CGD may exert a negative effect on HSPC and their transduction, thereby increasing the risk of oncogenesis,[8] further emphasize the need to improve the efficacy and safety of the GT platforms used to treat X-CGD.

The limited cargo capacity of viral vectors also contributes to the many challenges of achieving clinically relevant yet tight physiological expression and regulation of a transgene. Transgene size has hampered the production of high-titer lentiviral vectors in diseases such as CGD and β-thalassemia, in which the endogenous locus control region is too big to be included within the viral vector, making obtaining sufficient levels of transgene expression challenging. Several groups have developed transduction enhancers that could, in principle, result in sufficient transgene copies even with low-titer vectors.[9] Here, thanks to the bioinformatics-guided design of a lentiviral vector to express CYBB gene from a minimal endogenous enhancer-promoter region, Wang et al have achieved increased transduction levels while preserving physiological expression of the corrective gene. The enhancer-promoter optimization has allowed Wang et al to significantly reduce the cargo size, thus improving vector titers and transduction efficacy that contribute, together with the improved expression profiles, to functional restoration of immune cells deriving from modified HSPC. This level of fine regulation could reduce the risk associated with non-physiological levels of gp91$^{phox}$ expression in HSPC potentially triggering aberrant reactive oxygen species production.[2] The newly designed vector