pretenders, especially in cases who do not carry the *FAS* mutation or have an atypical clinical presentation.[5-7]

Molnár et al retrospectively collected clinical, immunological, and genetic data from 215 patients with a clinical suspicion of ALPS. They divided patients into 3 clinical groups (definite, suspected, or unlikely ALPS) based on an updated ALPS 2010 diagnostic protocol (updated according to the 2019 working definitions of the European Society for Immunodeficiencies). Consistent with previous reports, the authors observed significantly higher αβ-DNTs in all patients with definite ALPS (median, 3.95%; range, 1.8% to 23.0%), although the positive predictive value of this test remained low by itself. An abnormal in vitro apoptosis assay was highly specific for patients with definite ALPS and was also the only biomarker that showed a significant difference between the definite and suspected ALPS groups. Although this test is not widely available and may be unsuitable for routine clinical use, it continues to be a valuable aid in diagnosis and management of these patients.

Given these challenges, the authors sought to define an optimal biomarker combination of αβ-DNTs, in vitro apoptosis assay, and sFASL level. Although all combinations showed a significant difference between the definitive and unlikely ALPS groups, the authors found that normal αβ-DNTs and a normal in vitro apoptosis assay could essentially rule out ALPS (see table). The caveat is that they were unable to evaluate the sensitivity or specificity of additional biomarkers combinations, such as immunoglobulin G, vitamin B-12, IL-10, and IL-18, because of a very small number of available samples. Additionally, they were unable to define a biomarker combination to differentiate between the definite and suspected ALPS groups.

The limitations of the study include its retrospective nature, lack of availability of outcome data, inability to correlate specific abnormal biomarkers with clinical presentation, and missing information on treatment received and disease course. The authors were also not able to evaluate the sensitivity or specificity of biomarkers such as vitamin B12 level and others. However, the findings of this study do support the value of the biomarkers defined in revised 2010 diagnostic criteria for ALPS and provide data on additional reliable biomarker combinations that could expedite the diagnosis and treatment of patients with ALPS, without waiting for a genetic diagnosis. This report provides valuable criteria with which to define patients who truly have ALPS and those who do not.

Conflict-of-interest disclosure: K.L.M. is a member of the medical advisory committee for SOBI. N.G. declares no competing financial interests. ■

REFERENCES

1. Molnár E, Radwan N, Kovacs G, et al. Key diagnostic markers for autoimmune lymphoproliferative syndrome with molecular genetic diagnosis. *Blood*. 2020;136(17):1933-1945.
2. Rao VK, Oliveira JB. How I treat autoimmune lymphoproliferative syndrome. *Blood*. 2011; 118(22):5741-5751.
3. Rieux-Laucat F, Fischer A, Deist FL. Cell-death signaling and human disease. *Curr Opin Immunol*. 2003;15(3):325-331.
4. Bleesing JJ. Autoimmune lymphoproliferative syndrome (ALPS). *Curr Pharm Des*. 2003;9(3): 265-278.
5. Caminha I, Fleisher TA, Hornung RL, et al. Using biomarkers to predict the presence of FAS mutations in patients with features of the autoimmune lymphoproliferative syndrome. *J Allergy Clin Immunol*. 2010;125(4): 946-949.e6.
6. Magerus-Chatinet A, Stolzenberg MC, Loffredo MS, et al. FAS-L, IL-10, and double-negative CD4- CD8- TCR alpha/beta+ T cells are reliable markers of autoimmune lymphoproliferative syndrome (ALPS) associated with FAS loss of function. *Blood*. 2009;113(13):3027-3030.
7. Rensing-Ehl A, Janda A, Lorenz MR, et al. Sequential decisions on FAS sequencing guided by biomarkers in patients with lymphoproliferation and autoimmune cytopenia. *Haematologica*. 2013;98(12):1948-1955.
8. Oliveira JB, Bleesing JJ, Dianzani U, et al. Revised diagnostic criteria and classification for the autoimmune lymphoproliferative syndrome (ALPS): report from the 2009 NIH International Workshop. *Blood*. 2010;116(14):e35-e40.

DOI 10.1182/blood.2020007418

LYMPHOID NEOPLASIA

Comment on Patel et al, page 1946

Cost-effectiveness targeting CLL

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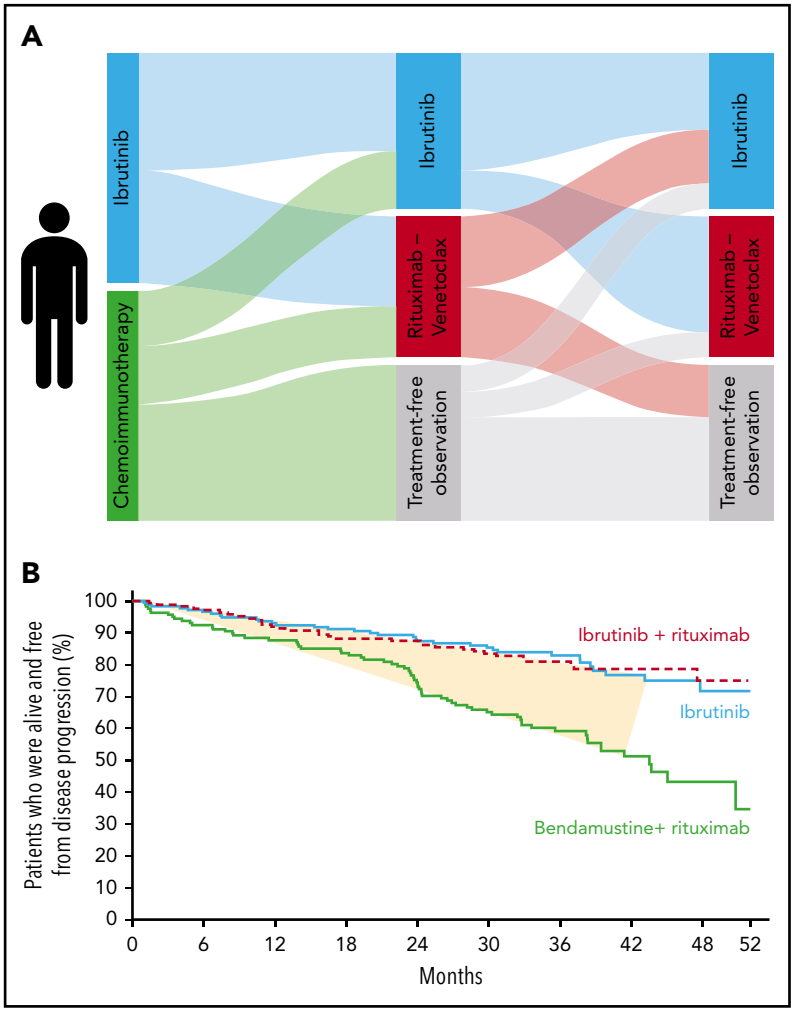
In this issue of *Blood*, Patel and colleagues have calculated that the price of ibrutinib should be reduced by 72% to be cost-effective as first-line therapy for patients with chronic lymphocytic leukemia (CLL).[1]

Targeted therapy has become a mainstay of CLL treatment. An abundance of treatment options, including combination approaches, are being tested in clinical trials. Thus, an evaluation of the cost-effectiveness of the different sequences of currently approved therapies is warranted. The cost of an extra quality-adjusted life-year was modeled based on published data from the phase 3 ALLIANCE study.[2] Although superiority, in terms of progression-free survival, was demonstrated for ibrutinib-based therapy vs bendamustine plus rituximab, the cost of 1 additional quality-adjusted life-year was calculated to be $2 350 041. When restricting the use of ibrutinib as first-line therapy to patients with more aggressive disease in terms of IGHV-unmutated status, the price tag was $1 373 500 per quality-adjusted life-year.

Results from 4 pivotal clinical trials in CLL, comparing targeted therapy vs chemoimmunotherapy in the front-line setting, were published in 2019. The iLLUMINATE trial[3] and the CLL14 trial[4] compared ibrutinib plus obinutuzumab and venetoclax plus obinutuzumab, respectively, vs chlorambucil plus obinutuzumab for patients with significant comorbidities. The ALLIANCE study[2] compared ibrutinib, with or without rituximab, vs bendamustine plus rituximab for patients older than 65 years of age, whereas the E1912 study[5] compared ibrutinib plus rituximab vs fludarabine, cyclophosphamide, and rituximab for patients younger than 70 years of age. All 4 trials met their primary outcome and demonstrated superiority in terms of longer progression-free survival for targeted therapy of CLL in the front-line setting. Thus,



Treatment trajectories and outcome for patients with CLL. (A) The possible treatment paths for a patient with CLL meeting the criteria for treatment. (B) An example Kaplan-Meier curve for progression-free survival from the study forming the basis for cost-effectiveness analyses by Patel et al; the fraction of patients truly benefitting from targeted therapy is shaded in yellow.

the decision on front-line treatment in CLL might be considered apparent and easy when discussing your patient's treatment path among the options illustrated (see figure): targeted therapy rather than chemoimmunotherapy. This is what most current clinical guidelines recommend.

However, the answer may not be that straightforward. As clearly demonstrated by Patel and colleagues, the cost for a gained quality-adjusted life-year may be higher than what is acceptable for our society. As they put it, "The monthly cost of ibrutinib would need to be decreased by at least 72% for first-line ibrutinib to be cost-effective." Medical ethical standards differ between countries; however, in most countries, those standards do not permit the socioeconomic standing of the patient to impact (ie, limit) equal access to treatment. Ensuring the fair distribution of health resources is part of the responsibility of medical providers. This pinpoints the importance of developing new structures for price setting of pharmacological treatment, in general, and antineoplastic treatment, in particular. The lack of correlation between monthly treatment costs and clinical benefit for approved antineoplastic treatment emphasizes the need for a new price structure.[6] Thus, health care payers, whether privately or publicly based, and pharmaceutical companies should join forces to address this issue.

A second issue concerning cost-effectiveness is indirectly addressed by Patel and colleagues: only a minority of patients actually benefit from targeted therapy. The patients in the yellow-shaded area between the 2 graphs are the ones experiencing an improved outcome upon targeted therapy vs chemoimmunotherapy (see figure). The patients below the yellow-shaded part did well independent of treatment path, whereas the patients above the yellow-shaded part did not benefit from either treatment, because they progressed within the first 3 years. Thus, we need personalized treatment. Essentially, we should give the right treatment to the right patient at the right time. The price tag per quality-adjusted life-year could be lowered to $1 373 500 by restricting targeted front-line therapy to patients with more aggressive CLL in terms of IGHV-unmutated status. Although still far away from the willingness-to-pay limit of $150 000 per quality-adjusted life-year, this would be a first step toward personalized treatment for CLL in the front-line setting. More than half of patients with CLL and IGHV-mutated status experience long-lasting remissions and, perhaps, even a cure.[7] This is reflected by a negative quality-adjusted life-year gain upon ibrutinib vs chemoimmunotherapy for this patient group.

To smartly use targeted therapy approaches in CLL, we should combine molecular and genetic omics data with data assembled in electronic health care records. These so-called "big data" could improve the identification of patients at the highest chance of benefitting from a specific treatment approach. The impact of recurrent mutations in CLL has been detailed since the publishing of 2 landmark papers on the genetic landscape of CLL in 2015.[8,9] The utilization of data from electronic health care records has recently been applied to identify newly diagnosed patients with CLL who are at high risk for infection or early need of treatment by an ensemble machine learning approach.[10] By combining such approaches, we can improve cost-effectiveness and treatment decisions, paving the path toward truly personalized treatment.

Patel and colleagues have informed the discussion of cost-effectiveness for targeted therapy of CLL. In summary, they demonstrate that the price setting for ibrutinib should be lowered by 72% to reach the willingness-to-pay threshold of $150 000 per quality-adjusted life-year.

Furthermore, their analyses emphasize the need for personalized treatment, because patients with IGHV-mutated CLL demonstrated a loss of quality-adjusted life-years upon treatment with ibrutinib vs chemoimmunotherapy in the front-line setting. Thus, stringent

cost-effectiveness analyses based on published clinical trial data with subgroup analyses defined by omics and "big data" should be encouraged by health authorities and the scientific community.

Conflict-of-interest disclosure: C.U.N. has received research grants/funding from AbbVie, AstraZeneca, Janssen, the Danish Cancer Society, and the Novo Nordisk Foundation and has received consultancy fees and/or travel grants from Janssen, AbbVie, Novartis, Roche, Sunesis, Gilead Sciences, AstraZeneca, and CSL Behring. ■

REFERENCES

1. Patel KK, Isufi I, Kothari S, Davidoff AJ, Gross CP, Huntington SF. Cost-effectiveness of first-line versus third-line ibrutinib in patients with untreated chronic lymphocytic leukemia. *Blood*. 2020;136(17):1946-1955.
2. Woyach JA, Ruppert AS, Heerema NA, et al. Ibrutinib regimens versus chemo-immunotherapy in older patients with untreated CLL. *N Engl J Med*. 2018;379(26):2517-2528.
3. Moreno C, Greil R, Demirkan F, et al. Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (iLLUMINATE): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2019;20(1):43-56.
4. Fischer K, Al-Sawaf O, Bahlo J, et al. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. *N Engl J Med*. 2019;380(23):2225-2236.
5. Shanafelt TD, Wang XV, Kay NE, et al. Ibrutinib-rituximab or chemoimmunotherapy for chronic lymphocytic leukemia. *N Engl J Med*. 2019;381(5):432-443.
6. Vokinger KN, Hwang TJ, Grischott T, et al. Prices and clinical benefit of cancer drugs in the USA and Europe: a cost-benefit analysis. *Lancet Oncol*. 2020;21(5):664-670.
7. Fischer K, Bahlo J, Fink AM, et al. Long-term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: updated results of the CLL8 trial. *Blood*. 2016; 127(2):208-215.
8. Landau DA, Tausch E, Taylor-Weiner AN, et al. Mutations driving CLL and their evolution in progression and relapse. *Nature*. 2015; 526(7574):525-530.
9. Puente XS, Beà S, Valdés-Mas R, et al. Non-coding recurrent mutations in chronic lymphocytic leukaemia. *Nature*. 2015;526(7574):519-524.
10. Agius R, Brieghel C, Andersen MA, et al. Machine learning can identify newly diagnosed patients with CLL at high risk of infection. *Nat Commun*. 2020;11(1):363.

DOI 10.1182/blood.2020006949

PLATELETS AND THROMBOPOIESIS

Comment on Sims et al, page 1956

Gray platelet syndrome: immunity goes awry

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In this issue of *Blood*, Sims et al[1] describe clinical, genotypic, and phenotypic findings in 47 patients with the gray platelet syndrome (GPS), a rare recessive platelet disorder with α-granule abnormalities and mutations in *NBEAL2*. They expand the repertoire of granule defects in GPS to leukocytes and document an important association of GPS with immune dysregulation and autoimmune diseases.

GPS is a heterogeneous bleeding disorder characterized by macrothrombocytopenia and selective deficiency of α granules and their contents. The name derives from the initial observation of gray appearance of platelets with a paucity of granules on blood films from a patient with a lifelong bleeding disorder. Other features include splenomegaly, myelofibrosis, and emperipolesis with neutrophils within megakaryocytes in the bone marrow. In 2011, 3 groups reported recessive variants in *NBEAL2* as the cause for GPS.[2] NBEAL2 is a BEACH-domain–containing protein linked to granule development. GPS has hitherto been considered essentially a platelet disorder. The current study, involving the largest cohort of 47 GPS patients studied to date, provides major insights on multiple aspects of GPS and *NBEAL2*.

From the perspective of the GPS disease, there are several findings, including the marked heterogeneity in *NBEAL2* variants (70 etiological variants, 32 novel) and bleeding symptoms (5 patients had none), and the high prevalence of cytopenia of at least 1 leukocyte type (77% of patients), elevated B12 levels (91%), and bone marrow fibrosis (57%). Emperipolesis was noted in 58% of megakaryocytes in 3 GPS bone marrows studied (1% in controls). There was no association of granulocyte or monocyte cytopenia or of splenomegaly with BM fibrosis. There were no significant genotype-phenotype associations observed.

Selective platelet α-granule deficiency has been the hallmark of GPS. The current study extends the abnormalities associated with *NBEAL2* mutations to multiple immune cells. The authors found decreased counts of neutrophils, monocytes, lymphocytes, eosinophils, and basophils in GPS patients and provide evidence of alteration in granules and their proteins.

Detailed studies document striking alterations in the transcriptome and proteome profiles in not only platelets but also neutrophils, monocytes, and $CD4^+$ T cells and provide convincing evidence of a critical role for NBEAL2 in granule formation, spanning multiple blood cells. These findings implicating an effect on leukocytes are in line with studies in $Nbeal2^{-/-}$ mice.[3,4] Of the differentially abundant proteins in platelets, neutrophils, and monocytes, Sims et al found that 89%, 86%, and 62%, respectively, were reduced in GPS patients, and they were enriched in granule proteins. Nine such proteins were reduced across at least 3 cell types. Interestingly, besides the expected decrease in α-granule proteins, GPS platelets had increased levels of 13 proteins, 5 of which are recognized neutrophil granule proteins, revealing platelet enrichment in neutrophil constituents.

A major finding in this study is the recognition of autoimmunity, autoantibody production, and inflammation in GPS patients, indicating the clinical consequences of the immune cell abnormalities. Autoimmune or infectious complications have been previously observed in a few GPS patients, and *Nbeal2*-deficient mice have increased susceptibility to infection or its complications.[3,4] The current study identified an autoimmune disease diagnosis in 26% of GPS patients, including Hashimoto thyroiditis, rheumatoid arthritis, and atypical autoimmune lymphoproliferative syndrome (see figure). Mass spectrometry of plasma indicated an elevated acute