$P < .001$) with 75% of patients in the KRdc group achieving MRD negativity (MFC, 4×10^{-5}) post-ASCT.[8] Findings from the ongoing FORTE trial also demonstrated the efficacy of the KRd-ASCT regimen; this phase 3 randomized study compared 4 KRd cycles followed by ASCT and 4 KRd consolidation cycles (n = 158); 4 carfilzomib, cyclophosphamide, and dexamethasone (KCd) cycles followed by ASCT and 4 KCd consolidation cycles (n = 159); or 12 KRd cycles (n = 157). Patients in the KRd-transplant arm had a 1-year sustained undetectable MRD rate of 68% of patients compared with 54% in the nontransplant arm ($P = .02$). With a median follow-up of 45 months, the estimated 3-year PFS was 78% in the transplant arm vs 66% in the nontransplant arm ($P = .023$).[9]

With the high MRD-negativity rate associated with triplet induction and ASCT, the current question is whether the addition of anti-CD38 monoclonal antibodies (daratumumab [Dara]-KRd or isatuximab-KRd) can further improve depth and duration of response and translate to improved survival, obviating the need for ASCT. Preliminary results with the Dara-KRd quadruplet report an MRD^- rate of 83% without ASCT.[10] We eagerly await the findings of the ADVANCE trial (NCT04268498), which will compare Dara-KRd with KRd or VRd and the phase 3 COBRA study (NCT03729804) comparing extended KRd (24 cycles) with the established RVd regimen (8 cycles with lenalidomide maintenance) in high-risk patients with deferred ASCT.

The utility and achievement of MRD negativity during maintenance therapy has also yet to be well defined. Can patients with sustained MRD^- sCR cease maintenance therapy without the risk of early relapse? A risk and MRD-adaptive approach in the intensification or de-escalation of treatment is still under investigation and will help to guide clinical decisions in the future. Until then, this study demonstrates that KRd induction/consolidation with ASCT achieves deep and durable responses with a manageable safety profile and is a future option for the upfront treatment of TE patients with NDMM.

Conflict-of-interest disclosure: S.J.H. provided consultancy services to, served on an advisory board for, and was an investigator on studies for AbbVie; provided consultancy services to, received honoraria from, served on advisory boards for, received research funding from, and was an investigator on studies for Amgen, Celgene, Janssen Cilag, and Novartis; provided consultancy services to and served on advisory boards for GlaxoSmithKline; provided consultancy services to, received honoraria from, served on advisory boards for, and was an investigator on studies for Roche/Genentech; provided consultancy services to, received honoraria from, and served on advisory boards for Takeda; served on scientific advisory boards for, received research funding from, and was an investigator on studies for Haemalogix; and provided consultancy services to/held an advisory role with Sanofi. J.E. declares no competing financial interests. ■

REFERENCES

1. Roussel M, Lauwers-Cances V, Wuilleme S, et al. Up-front carfilzomib, lenalidomide, and dexamethasone with transplant for patients with multiple myeloma: the IFM KRd final results. *Blood*. 2021;138(2):113-121.
2. Munshi NC, Avet-Loiseau H, Rawstron AC, et al. Association of minimal residual disease with superior survival outcomes in patients with multiple myeloma: a meta-analysis. *JAMA Oncol*. 2017;3(1):28-35.
3. Attal M, Lauwers-Cances V, Hulin C, et al.; IFM 2009 Study. Lenalidomide, bortezomib, and dexamethasone with transplantation for myeloma. *N Engl J Med*. 2017;376(14):1311-1320.
4. Kuhn DJ, Chen Q, Voorhees PM, et al. Potent activity of carfilzomib, a novel, irreversible inhibitor of the ubiquitin-proteasome pathway, against preclinical models of multiple myeloma. *Blood*. 2007;110(9):3281-3290.
5. Dimopoulos MA, Goldschmidt H, Niesvizky R, et al. Carfilzomib or bortezomib in relapsed or refractory multiple myeloma (ENDEAVOR): an interim overall survival analysis of an open-label, randomised, phase 3 trial. *Lancet Oncol*. 2017;18(10):1327-1337.
6. Kumar SK, Jacobus SJ, Cohen AD, et al. Carfilzomib or bortezomib in combination with lenalidomide and dexamethasone for patients with newly diagnosed multiple myeloma without intention for immediate autologous stem-cell transplantation (ENDURANCE): a multicentre, open-label, phase 3, randomised, controlled trial. *Lancet Oncol*. 2020;21(10):1317-1330.
7. Jasielec JK, Kubicki T, Raje N, et al. Carfilzomib, lenalidomide, and dexamethasone plus transplant in newly diagnosed multiple myeloma. *Blood*. 2020;136(22):2513-2523.
8. Jackson GH, Pawlyn C, Cairns DA, et al.; UK NCRI Haemato-oncology Clinical Studies Group. Carfilzomib, lenalidomide, dexamethasone, and cyclophosphamide (KRdc) as induction therapy for transplant-eligible, newly diagnosed multiple myeloma patients (Myeloma XI+): interim analysis of an open-label randomised controlled trial. *PLoS Med*. 2021;18(1):e1003454.
9. Gay F, Musto P, Rota Scalabrini D, et al. Survival analysis of newly diagnosed transplant eligible multiple myeloma patients in the randomized Forte trial [abstract]. *Blood*. 2020;136(suppl 1):35-37. Abstract 731.
10. Landgren O, Hultcrantz M, Lesokhin AM, et al. Weekly carfilzomib, lenalidomide, dexamethasone and daratumumab (wKRd-D) combination therapy provides unprecedented MRD negativity rates in newly diagnosed multiple myeloma: a clinical and correlative phase 2 study [abstract]. *Blood*. 2019;134(suppl 1):862. Abstract 653.

DOI 10.1182/blood.2021011751

LYMPHOID NEOPLASIA

Comment on Parikh et al, page 149

CLL-IPI: valid in the era of oral inhibitors?

Nadine Kutsch | University of Cologne

In this issue of *Blood*, Parikh et al[1] show in their analysis for the first time that the chronic lymphocytic leukemia international prognostic index (CLL-IPI) can predict time to first diagnosis and overall survival (OS) in a cohort of 969 patients with monoclonal B-cell lymphocytosis (MBL) and Rai 0 stage CLL. This might prove to be a very useful tool for the management of these classical watch-and-wait patients who need to be monitored for progression or disease-related symptoms and potential treatment indication on a regular basis.

The CLL-IPI[2] is a well-established score in CLL and was originally developed based on data from 8 phase 3 studies including 3472 treatment-naive patients with CLL.

It discriminates 4 prognostic subgroups with different 5-year overall survival rates resulting in different treatment implications and combines the parameters TP53 status, IGHV mutational status, serum β2-microglobulin concentration, clinical stage, and age, with different weighting in a prognostic score. The CLL-IPI was initially introduced in 2016 and comprises data of patients who received chemoimmunotherapy.[2]

A plethora of other prognostic scores with focus on different clinical outcome parameters like OS, progression-free survival, or treatment-free survial have been introduced to the field of CLL research, but a meta-analysis by the Cochrane group recently revealed that the CLL-IPI still shows the best discrimination, despite overestimation.[3]

However, the treatment landscape in CLL has dramatically changed in the last years with the introduction of novel oral inhibitors. Against the background of quickly changing treatment possibilities and recommendations, the CLL-IPI might be outdated now. Therefore, several further scores have been introduced to the new treatment landscape.

Soumerai et al[4] developed the first validated risk score to predict OS in patients with relapsed/refractory CLL who were treated with targeted therapies. It identified 4 factors that differ widely from the CLL-IPI including serum β2-microglobulin, lactate dehydrogenase, hemoglobin, and time from initiation of last therapy and helps to identify patients who are at a high risk for early death.

The BALL score identifies a subset of patients with CLL, accounting for about 50% of the whole population, who benefit, in particular, from single agent ibrutinib. It comprises β2-microglobulin, hemoglobin, lactate dehydrogenase, and time elapsed from last therapy <24 months as parameters.[5] However, this score did not show satisfying results in a real-world patient cohort, so the improved survival risk score for ibrutinib, which excludes time to last therapy, was then developed to determine OS in relapsed/refractory patients with CLL treated with ibrutinib.[6]

Furthermore, a 4-factor model consisting of TP53 status, prior treatment, β-2 microglobulin, and lactate dehydrogenase levels was introduced. It identifies patients with an increased risk of ibrutinib failure at treatment initiation and remained significant when applied to either treatment-naive or relapsed/refractory patient cohorts treated with ibrutinib.[7]

In a completely different approach paying tribute to the changing dynamics within the course of the disease, the continuous individualized risk index was evaluated in CLL including the CLL-IPI and minimal residual disease levels. This dynamic risk model seems to be superior to established risk assessment scores in determining clinical outcomes.[8] However, this model is probably too complex to be used broadly in clinical practice but could be a very helpful tool in clinical trials otherwise. Prospectively, an easy-to-use tool will have to be developed for a more individualized management of patients that can be easily implemented into clinical routine and therefore finds broad acceptance. Hence, the CLL-IPI should be reevaluated as soon as more mature data on first-line treatments with oral inhibitors are available.

Conflict-of-interest disclosure: N.K. has received research funding and travel support from Gilead Sciences, Inc, and received travel support from Janssen and Celgene. ■

REFERENCES

1. Parikh SA, Rabe KG, Kay NE, et al. The CLL International Prognostic Index predicts outcomes in monoclonal B-cell lymphocytosis and Rai 0 CLL. *Blood*. 2021;138(2):149-159.
2. International CLL-IPI working group. An international prognostic index for patients with chronic lymphocytic leukaemia (CLL-IPI): a meta-analysis of individual patient data. *Lancet Oncol*. 2016;17(6):779-790.
3. Kreuzberger N, Damen JA, Trivella M, et al. Prognostic models for newly-diagnosed chronic lymphocytic leukaemia in adults: a systematic review and meta-analysis. *Cochrane Database Syst Rev*. 2020;7:CD012022.
4. Soumerai JD, Ni A, Darif M, et al. Prognostic risk score for patients with relapsed or refractory chronic lymphocytic leukaemia treated with targeted therapies or chemoimmunotherapy: a retrospective, pooled cohort study with external validations. *Lancet Haematol*. 2019;6(7):e366-e374.
5. Molica S, Baumann TS, Lentini M, Levato L, Delgado J, Montserrat E. The BALL prognostic score identifies relapsed/refractory CLL patients who benefit the most from single-agent ibrutinib therapy. *Leuk Res*. 2020;95:106401.
6. Gentile M, Morabito F, Del Poeta G, et al. Survival risk score for real-life relapsed/refractory chronic lymphocytic leukemia patients receiving ibrutinib. A campus CLL study. *Leukemia*. 2021;35(1):235-238.
7. Ahn IE, Tian X, Ipe D, et al. Prediction of outcome in patients with chronic lymphocytic leukemia treated with ibrutinib: development and validation of a four-factor prognostic model. *J Clin Oncol*. 2021;39(6):576-585.
8. Kurtz DM, Esfahani MS, Scherer F, et al. Dynamic risk profiling using serial tumor biomarkers for personalized outcome prediction. *Cell*. 2019;178(3):699-713.

DOI 10.1182/blood.2021011937

THROMBOSIS AND HEMOSTASIS

Comment on Silasi et al, page 178

FXII inhibition: multipronged benefits

Helen Philippou | University of Leeds

In this issue of *Blood*, Silasi et al[1] identified that inhibition of activated factor XII (FXIIa) using an antibody (5C12) reduces the activation of coagulation and the kallikrein-kininogen pathways, induced by heat-inactivated *Staphylococcus aureus* (HI-SA). Furthermore, by inhibiting FXII function, there was decreased activation of complement and inflammatory cytokines, resulting in preserved organ function and survival of baboons subject to a challenge with HI-SA. These findings suggest potential benefit of prophylactic treatment of patients at increased risk of pathological coagulation and inflammatory responses using an inhibitor of FXIIa. Such indications include prevention of sepsis or its mitigation in severe infections in which FXIIa activity is involved in its pathogenesis.

For many years, the role of FXII in coagulation was not understood, until Renne et al[2] discovered that FXII plays an essential role in the propagation phase of