a standard of care for previously treated patients based on data from phase 3 trials demonstrating superior progression-free survival (PFS) and overall survival (OS) as compared with standard therapies.\(^2,3\) Although limited data exists for these agents in previously untreated disease, preliminary data with ibrutinib is especially provocative, with an estimated 96% PFS at 33 months.\(^4\) Clinical studies such as the intergroup trial E1912 (#NCT02048813) are ongoing to compare these novel agents to standard FCR in the upfront setting, so this is a particularly fitting time for an update on the long-term experience with FCR.

The current article reports on 5.9 years of follow-up from treatment with either fludarabine and cyclophosphamide (FC) or FCR, with an emphasis on late-term adverse events as well as efficacy of the regimens. Not surprisingly, FCR remains superior to FC. In the FCR group, median PFS was 56.8 months and OS has not yet been reached. Late-onset malignancies are highlighted and include a 4.7% incidence of Richter transformation and 1.6% incidence of myelodysplastic syndrome/acute myeloid leukemia (MDS/AML). Myeloid neoplasia was not different between the groups; however, there was a higher incidence of Richter in the FC arm. Solid tumors were observed at a similar rate to the general population. This incidence of MDS/AML is lower than has been reported by the MD Anderson group with FCR,\(^5,6\) perhaps relating to the duration of follow-up. It has yet to be determined how these long-term toxicities compare with kinase inhibitors, but this will be an important question for the future.

This study also addresses genomic risk groups that are pertinent to chemoimmunotherapy. Patients with unmutated immunoglobulin heavy chain variable region (IGHV), del(17p), del(11q), high thymidine kinase, mutated TP53, and mutated SF3B1 all show superior PFS for FCR compared with chlorambucil.\(^7\) Multiple publications have shown no advantage of fludarabine over chlorambucil in older patients,\(^8,9\) and preliminary results from the recent German CLL Study Group (ie, GCLLSG10 study) of FCR vs bendamustine/rituximab show superior PFS for FCR except for patients age 65 years of greater, where the two regimens appear equivalent.\(^9\) Early toxicities with FCR and secondary malignancies, which may be more common or less treatable in the elderly, make less intensive regimens of significant interest for this group.

The long-term data presented in this study, especially when taken together with the data from MD Anderson, strongly suggest that some low-risk patients are being cured with FCR chemoimmunotherapy, and this regimen should be offered to young, fit patients who do not wish to participate in a clinical trial. Important open questions remain, however. With excellent options for second-line therapy with kinase inhibitors, is it imperative to choose the frontline therapy with the longest PFS, or is frontline therapy with less toxicity more desirable in some circumstances? As well, if kinase inhibitors become an option for frontline therapy, does the potential for cure and therapy interruption outweigh the risks of short- and long-term toxicity? As we move forward with an increasing armamentarium of targeted therapies in CLL, these questions will become more relevant, and future clinical trials will be needed to address these. The fact that these questions exist, though, highlight how far the field of CLL therapy has advanced over the past decade and should instill hope for our CLL patients in the years to come.

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DOI 10.1182/blood-2015-11-678557

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**IMMUNOBIOLOGY**

Comment on Volpi et al, page 216

**The sting of WASP deficiency: autoimmunity exposed**

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In this issue of *Blood*, Volpi and colleagues have further dissected the role of B lymphocytes in autoimmune reactions using a murine model for Wiskott-Aldrich syndrome (WAS) and identified a novel potential therapeutic target, which may have implications not only for this disease but also other causes of autoimmunity.\(^1\)
Primary immunodeficiencies (PIDs) are rare inborn errors, predominantly inherited in a recessive fashion, in which persistent or recurrent infection, often due to opportunistic pathogens, is a major manifestation. As we understand more about normal immune function by studying the effects of these rare genetic mutations in patients, so our awareness of the potential presentations of such patients has evolved. Autoimmunity coexists with infectious manifestations in conventional PIDs (eg, Omenn syndrome, FOXP3 deficiency, AIRE deficiency), but increasingly autoimmune manifestations are recognized as the major symptom of newly described primary immunodeficiencies. Examples include patients with mutations in ITCH, CTLA4, and tripeptidyl-peptidase II, and autosomal dominantly inherited gain-of-function signal transducer and activator of transcription-1.

Increased autoimmunity in Wiskott-Aldrich–deficient (WKO) and B/WcKO mice compared to mice with WASP- and N-WASP–deficient B-lymphocytes (B/DcKO). (A) Protein array detection of a range of IgG autoantibodies in B/WcKO (column 4) and B/DcKO (column 5) mice, demonstrated by net fluorescence intensity ratios between each mouse (range from 0 [negative; blue] to 1 [black] to 5 [positive; yellow]). A systemic lupus erythematosus (SLE) control model (column 1) and B/WcKO mice demonstrate numerous positive autoantibodies compared with B/DcKO mice. (B) Histologic examination of formalin-fixed, paraffin-embedded kidney sections from WKO and B/WcKO mice demonstrating severe hypercellularity and capillary wall thickening, not seen in wild-type (WT) and B/DcKO mice. (C) Blind scoring of glomerular damage (range from 0 = no glomerular pathology to 3 = severe glomerular pathology) confirming significant renal damage in WKO and B/WcKO mice, compared with WT and B/DcKO mice. Statistical significance assessed by Mann-Whitney test (*P < .05, **P < .01, ***P < .001). See Figure 2B-D in the article by Volpi et al that begins on page 216.
they elegantly demonstrate that mice with WAS-deficient B lymphocytes (B/WcKO) display increased production of IgM and IgG autoantibodies (see figure, panel A) and had increased glomerular deposits of IgG leading to renal immunopathology, in contrast to mice with B/DcKO which lacked IgG autoantibodies and failed to develop renal disease (see figure, panels B–C). These findings suggest an important role for N-WASP in the development of autoimmune pathology in WAS patients, and thus identify an important potential therapeutic target. Although hematopoietic stem cell transplantation can effectively cure these patients, mixed donor chimerism increases the risk of autoimmune complications posttransplantation. The gene therapy offers an alternative curative pathway for these patients, but only partial function is restored in such patients, increasing the potential risk of late-occurring autoimmunity. Thus, identification of a novel and specifically directed therapeutic target may extend the treatment options available to this group of patients, before or after stem cell therapy. Given that autoantibody-driven autoimmune disease is commonly encountered among the general community, it may well be that such a target has widespread applicability in the general medical community.

Conflict-of-interest disclosure: The author declares no competing financial interests.

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DOI 10.1182/blood-2015-10-677237

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LYMPHOID NEOPLASIA

Comment on Scarfò et al, page 221

ALK-negative anaplastic large-cell lymphoma

Philippe Gaulard1 and Laurence de Leval2

In this issue of Blood, Scarfò et al describe a novel subset of anaplastic lymphoma kinase (ALK)-negative anaplastic large-cell lymphoma (ALCL) associated with aberrant expression of ERBB4 transcripts and potential clinical relevance.

ALCLs represent a subset of peripheral T-cell lymphomas (PTCLs) defined by a proliferation of large lymphoid cells, referred to as hallmark cells, with strong expression of CD30. The molecular deciphering of ALCL started in the 1990s, with the discovery of a recurrent t(2;5)(p23;q35) translocation fusing the ALK gene and the nucleophosmin (NPM) gene generating a NPM-ALK fusion protein in a subset of ALCL, and subsequent description...
The sting of WASP deficiency: autoimmunity exposed

Andrew R. Gennery