Three years of ibrutinib in CLL

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In this issue of Blood, Byrd et al provide an important update on the prolonged efficacy and the limited and reducing toxicity of the single-agent Bruton tyrosine kinase inhibitor ibrutinib in chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma patients who are followed for a median time of 3 years from start of treatment.1

The study confirms and extends previous results2 but also adds new observations for future larger investigations, particularly in treatment-naive patients. The data continue to demonstrate that ibrutinib promotes a high response rate that improves in quality with time, leading to durable remissions in all genetic subsets of CLL patients. Duration of responses appear dramatic in treatment-naive patients, who carry a lower incidence of genetic damages than relapsed/refractory CLL patients.1 Unlike chemotherapy and chemoimmunotherapy regimens, which are given for a definite period because of limited tolerability, toxicities observed with continuous ibrutinib dosing appear modest, allowing most patients to remain on ibrutinib for an extended period (see figure).

One first important observation in this study is that quality of response gradually improves with duration of treatment. Ibrutinib induces death of 2.7% CLL cells per day in the lymph node, but a numerable fraction of cells is forced to exit and remain in the circulation.2-4 Ibrutinib is likely to interfere with other pathways associated with migration, adhesion, and egression.5 Inhibition in vitro occurs in those cells that have recovered from (super) antigen-induced anergy, and it is likely that the subgroup of cells with higher immunoglobulin (Ig)M and higher CXCR4 are those subject to ibrutinib-induced cell death.6

However, although immediate depletion of all CLL cells is not necessary, and best responses increase gradually during prolonged treatment, over 20% of treatment-naive patients suspend therapy within the first months.1 Because the median overall survival of patients who discontinue ibrutinib has been reported to be 3 months,7 it will be very important to further characterize the features of those patients who stop treatment and to identify strategies to anticipate failure or discontinuation for any reason. The prolonged lymphocytosis induced during ibrutinib treatment does not appear to associate with an increased risk of progression1; however, those circulating cells may go back to tissue, and disease can become more aggressive when ibrutinib is discontinued.2 The majority of relapsed/refractory patients who discontinue ibrutinib harbor high-risk features, including del(17p) and/or a complex karyotype.7 However, little is known about the characteristics of treatment-naive patients who suspend ibrutinib. It is of interest that the study by Byrd et al documents a different quality of response to ibrutinib in treatment-naive patients with CLL carrying unmutated (U) or mutated (M) tumor immunoglobulin gene heavy-chain variable (IGHV) region (see supplemental Table 3 in the article by Byrd et al1). In the initial report in the PCYC-1102 (NCT01105247) trial for relapsed/refractory patients, the only factor associated with a different overall response rate to ibrutinib was tumor IGHV mutation status, because only 33% of CLL patients with M-IGHV (M-CLL) vs 77% of CLL patients with U-IGHV (U-CLL) obtained a response.2 Although these differences do not remain after 3 years of treatment of relapsed/refractory patients, quality of response appears remarkably higher in treatment-naive patients with U-CLL (40% complete remission) vs M-CLL (6% complete remission).1 The number of treatment-naive patients is small for conclusions (n = 31) but advocates further investigations with longer follow-up and larger cohorts.

Another important observation is the gradual decrease of infection complications during the 3 years of treatment, despite the persistence of circulating tumor cells. Interestingly, grade ≥3 infections are virtually absent in treatment-naive patients.1 The authors point to the immune-modulating potential of ibrutinib through inhibition of interleukin-associated T-cell kinase, which can promote T helper cell type 1 CD4 T-cell outgrowth and diminish infection morbidity in animal models.1 However, CLL cells can act as regulatory B cells,8 and ibrutinib patients promote T helper cell type 1 CD4 T-cell outgrowth and diminish infection morbidity in animal models.1 However, CLL cells can act as regulatory B cells,8 and ibrutinib
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The figure summarizes the main findings of the report and shows how MPA can regulate T-cell proliferation and activation at different levels by targeting the interaction between TIF-IA and Ebp1, thus inhibiting rRNA synthesis and regulating the expression of key factors involved in cell proliferation, such as PCNA and p53. Moreover, this study suggests that the use of MPA together with sotrastaurin suppresses T-cell activation even more potently than each drug alone, by also inhibiting the TIF-IA–Ebp1 interaction.

Currently, MMF is used in combination with other drugs to treat certain autoimmune diseases, is part of the immunosuppressive regimen to modulate graft-versus-host disease following hematopoietic stem cell transplantation, and is used to prevent graft rejection post–organ transplantation. MMF is a produg of MPA, which is a purine analog. MPA inhibits specifically T-cell and B-cell activation and function by inhibiting the type II isofrom of inosine 5′-monophosphate dehydrogenase, a rate-limiting enzyme in the de novo synthesis of guanosine, thus depleting guanine nucleotides.2 Notably, previous studies by Huang et al, Dayton et al, and others have shown that MPA could also inhibit the synthesis of rRNA3,4; however, so far, the MPA mechanisms that could mediate this effect remain to be understood.

TIF-IA is involved in the regulation of rRNA synthesis and is expressed by all mammalian cells.5,6 In their recent work, Nguyen et al tested whether TIF-IA requires GTP binding in order to regulate RNA synthesis in T cells while interacting with other proteins. A systematic approach was used by the authors to assess the effects of MPA on cell lines, primary T cells, or cells from patients when possible, using chromatin immunoprecipitation assays and RNA analysis, and by knocking down or overexpressing the factor of interest.

Interestingly, they found that TIF-IA is a GTP-binding protein and that MPA treatment induced GTP depletion that then modified TIF-IA function and localization to the periphery of nucleolus into T cells, while blocking RNA polymerase I (Pol I) binding to the rDNA promoter. In addition, MPA treatment also led to increased p53 expression while decreasing PCNA expression, explaining how MPA can inhibit rRNA synthesis as well as proliferation in T cells. The investigators then went on to assess the role of Ebp1, which negatively regulates p53,7 and found that Ebp1 is upregulated in proliferating T cells and binds to TIF-IA. They showed that the interaction between TIF-IA and Ebp1 plays a key role in the regulation of cell proliferation and PCNA expression. In addition, they found that MPA reduced the interaction between TIF-IA and Ebp1 while upregulating p53 but decreasing PCNA expression, which suggests that the interaction between TIF-IA and Ebp1 might depend on TIF-IA binding to GTP.

It has been reported that Ebp1 can interfere with rRNA processing; however, whether Ebp1 regulates RNA synthesis was unknown. In the present study, the authors demonstrate for the first time that Ebp1 is key for TIF-IA retention where RNA synthesis occurs, and that both TIF-IA and Ebp1 play key roles in the regulation of rRNA. Moreover, phosphorylation at S360 of Ebp1 by protein kinase C 6 (PKCδ) is necessary for TIF-IA–mediated regulation of RNA synthesis. Interestingly, inhibiting phosphorylation of Ebp1 by using sotrastaurin, a specific inhibitor of PKCδ, together with MPA led to a very

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TIF-IA and Ebp1 regulate RNA synthesis in T cells

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