A Breakthrough Therapy in Relapsed Chronic Lymphocytic Leukemia: the Combination of Idelalisib and Rituximab

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Abstract
In a multi-center, randomized, double-blind, placebo-controlled phase III study reported in the New England Journal of Medicine [1], the combination of idelalisib and rituximab shows outstanding clinical activity as well as adequate safety in the treatment of relapsed chronic lymphocytic leukemia (CLL) patients.

Keywords: CLL, idelalisib, rituximab

Introduction

Chronic lymphocytic leukemia (CLL) is the second most common type of leukemia in adults and characterized by the accumulation of abnormal B-cells in blood, bone marrow, and secondary lymphoid organs [2]. The FCR (Fludarabine, Cyclophosphamide, Rituximab) regimen is the standard first-line chemotherapy for this incurable blood cancer; however, most CLL patients develop drug resistance and relapse. Relapsed CLL patients are generally ineligible to receive cytotoxic chemotherapy and they respond poorly to currently available therapies [3]. Therefore, identification of new therapies for this patient population is needed. Ibrutinib, a Bruton's tyrosine kinase (BTK) inhibitor, was recently approved for the treatment of CLL and mantle cell lymphoma (MCL) because of its significant clinical activity [4,5]. Another breakthrough therapy in relapsed CLL is the combination of idelalisib and rituximab which shows outstanding clinical activity as well as adequate safety in the treatment of relapsed CLL patients [1].

Rituximab is a monoclonal antibody targeting the protein CD20 which is primarily expressed on the surface of B cells. In addition to its use as a first-line agent, rituximab is also commonly used in treating relapsed CLL patients in combination with other therapeutic agents [6]; however, the duration of progression-free survival (PFS) is usually short and drug resistance often develops. Idelalisib, formerly named GS-1101 or CAL-101, is an oral, selective and reversible inhibitor of the p110 delta isoform of phosphoinositide-3-kinase (PI3Kδ) which mediates AKT activation in CLL cells [7,8]. As a single agent, or in combination with other drugs, idelalisib has shown significant activity with modest side effects in relapsed CLL patients in phase I and II studies [9,10].

In this multi-center, randomized, double-blind, placebo-controlled phase III study reported in the New England Journal of Medicine [1], 220 relapsed CLL patients were randomized into two groups. One group received rituximab and idelalisib (150 mg twice daily), and the other group was treated with rituximab and placebo. Compared to those treated with rituximab and placebo, patients who received the combination of rituximab and idelalisib had significantly improved median progression-free survival (not reached vs. 5.5 months), overall response (81% vs. 13%) and overall survival at 12 months (92% vs. 80%). Notably, patients bearing poor prognostic factors such as unmutated IGVH, TP53 mutations and 17p deletion also displayed improved progression-free survival upon rituximab plus idelalisib treatment. Both groups had similar rates of adverse events.

Following a positive interim evaluation, this study was stopped due to the exceptional activity of this combination in relapsed CLL patients so that all the trial patients could receive the idelalisib treatment. In consideration of the short follow-up in this study, the safety of rituximab plus idelalisib in long-term use requires further investigation. In addition, future studies of this combination in previously untreated CLL patients or other combinations of idelalisib with novel agents like Selinexor 11 in CLL will be of great interest. Overall, this phenomenal regimen shows a promising alternative treatment in relapsed CLL patients, and may shed light on the therapeutics of diverse B cell lymphomas. Interestingly, in the same issue of NEJM, a phase II study demonstrated that idelalisib showed significant activity in treating patients with relapsed indolent lymphoma 12.

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