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CASE REPORT

Concomitant imatinib and ibrutinib in a patient with chronic myelogenous leukemia and chronic lymphocytic leukemia

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Key Clinical Message

The availability of kinase and other small-molecule inhibitors to treat hematologic malignancies is increasing. Accordingly, novel regimens that employ these therapeutics are rapidly evolving. Herein we report the safe and effective administration of two targeted kinase inhibitors in a patient with concomitant chronic myelogenous leukemia and chronic lymphocytic leukemia.

Keywords

Ibrutinib, imatinib, leukemia, thrombocytopenia.

Introduction

Imatinib and ibrutinib are oral kinase inhibitors that, respectively, target the BCR-ABL1 fusion protein in chronic myelogenous leukemia (CML) and the Bruton's tyrosine kinase (BTK) in chronic lymphocytic leukemia (CLL) [1, 2]. Coexistence of these hematopoietic malignancies in an individual is rare [3]. Here, we report the co-administration of imatinib and ibrutinib in a patient who developed CML in a background of refractory CLL.

Case Report

The patient is a 67-year-old woman with a history of coronary artery disease and hypertension initially referred with generalized adenopathy, mild splenomegaly, a leukocyte count of 16,000 per cubic millimeter with lymphocytosis, and thrombocytopenia (platelet count, 25,000 per cubic millimeter). Flow cytometry of the blood showed a monoclonal population consistent with CLL (CD19+, CD20 low, lambda light chain low, CD5+, CD23+, CD38+, cytoplasmic ZAP-70+). Bone marrow biopsy demonstrated 50-70% infiltration with CLL and increased megakaryocytes. Cytogenetics by conventional G-banded chromosome analysis were normal, whereas florescence in situ hybridization (FISH) analysis demonstrated that 15% of the cells had *TP53* gene (17p13.1) deletion. Her presentation was thus consistent with Rai stage II disease and thrombocytopenia due to possible secondary immune thrombocytopenia (ITP). Treatment with oral prednisone for 1 week improved her platelet count to 144,000 per cubic millimeter, supporting a diagnosis of ITP. She proceeded to treatment with fludarabine, cyclophosphamide, and rituximab chemoimmunotherapy for six cycles with a good response (Fig. 1).

The patient was observed without treatment for approximately 3 years, but relapsed with a rising leukocyte count and worsening thrombocytopenia. Repeat FISH of the blood showed 17p13.1 deletion as well as 13q14.3 deletion. As part of a clinical trial evaluation for relapsed CLL, she underwent a bone marrow biopsy that demonstrated hypercellularity at 60% with trilineage hematopoiesis and

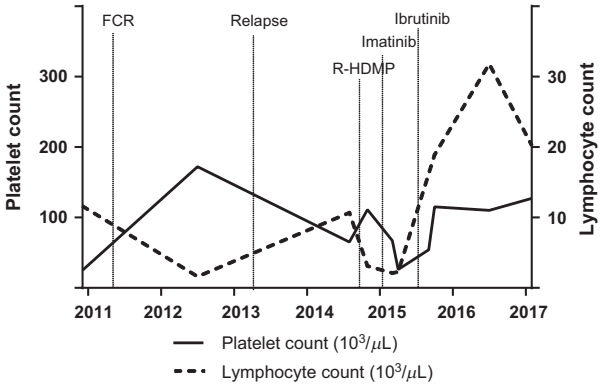

Figure 1. Effect of treatment on platelet and lymphocyte counts in a patient with CLL and CML over time. Timeline of the disease course with respect to therapeutic interventions and the lymphocyte and platelet counts. FCR (fludarabine, cyclophosphamide, and rituximab); R-HDMP (rituximab and high-dose methylprednisolone).

30% CLL infiltration. Surprisingly, G-banded chromosome analysis showed the presence of the Philadelphia chromosome with the translocation t(9;22)(q34;q11.2) that results in the *BCR-ABL1* gene fusion. FISH confirmed the *BCR-ABL1* gene fusion in 28% of cells. Evidence of CML disqualified the patient from the clinical trial, and she was instead treated with rituximab and high-dose methylprednisolone. Her platelet count and adenopathy improved, and she was started on imatinib 400 mg daily for CML. Dasatinib was avoided due to concern for cardiotoxicity in the setting of coronary artery disease. She achieved a major molecular response with a reduction in *BCR-ABL1* transcripts in the blood from 49.659% pretreatment to 0.191% after 3 months of therapy.

Despite the effectiveness of imatinib and monthly maintenance rituximab, the patient's platelet count subsequently decreased to 26,000 per cubic millimeter (Fig. 1). Physical examination remained stable, and a CT demonstrated an interval decrease in an index portacaval node from 2.4 × 1.3 cm to 1.9 × 0.7 cm. A repeat bone marrow biopsy showed a normocellular marrow with adequate trilineage hematopoiesis and megakaryocytes, but 15–20% CLL involvement. G-banded chromosome and FISH cytogenetic analyses for *BCR-ABL1* were negative, while transcripts remained detectable at 0.129%. Her dose of imatinib was lowered given concern that her worsening thrombocytopenia might be secondary to myelosuppression from imatinib, but the platelet count did not improve. Given the presence of CLL with 17p deletion and refractory thrombocytopenia, ibrutinib was initiated at 140 mg daily (to ensure tolerability in the setting of concomitant imatinib) and increased to 280 mg after 3 months. The patient has tolerated the combination of ibrutinib and imatinib well, and her only reported side effect is mild fatigue. Although she is requiring IVIG for hypogammaglobulinemia, her platelet count has stabilized at greater than 100,000 per cubic millimeter (Fig. 1) and her *BCR-ABL1* PCR is now undetectable.

Discussion

Combination chemotherapy has been a mainstay of treatment in oncology for more than half a century and relies upon on the synergistic cytotoxic effects of agents that eradicate proliferating cells. The identification of chromosomal aberrancies or driver mutations that alter discrete signaling pathways and fuel cellular transformation has led to the development of more precise and better tolerated therapies that target critical elements of these cascades. While the use of kinase inhibitors that inactivate BCR-ABL1 has proven effective in CML, this single-agent strategy ultimately revealed the development of novel mutations that can circumvent binding by these antagonists [4]. A similar experience with ibrutinib resistance is now being realized in CLL [5]. As the mechanisms of resistance in malignancies initially sensitive to a particular molecular compound are elucidated, the potential of employing more than one inhibitor may become attractive.

Although many of these agents are highly specific, their safety and impact on multiple downstream pathways when used in combination are poorly understood. For example, imatinib is known to impact several other kinases including c-KIT, PDGFR, and endogenous c-ABL [6]. Similarly, numerous non-BTK targets (both kinase and nonkinase) of ibrutinib have been identified, with as yet unclear clinical implications [7]. It is clearly important to be alert to any heretofore unknown effects of employing these powerful agents in combination.

Although the use of targeted molecular agents in combination necessitates caution, it may also open doors to the development of more efficacious chemotherapy regimens. Interestingly, imatinib has been shown to sensitize CLL cells to the cytotoxic effects of chlorambucil in vitro. In one study employing peripheral blood lymphocytes isolated from patients with CLL, imatinib's inhibition of c-ABL kinase activity led to decreased Rad51 phosphorylation, and thus decreased Rad51-mediated repair of chlorambucil-induced DNA damage [8]. In another study of peripheral blood lymphocytes from patients with CLL, imatinib alone was able to induce apoptosis in a subset of CLL cells at clinically relevant concentrations, with the level of c-ABL protein expression appearing to correlate with sensitivity to imatinib [9]. The possibility of a synergistic interaction between these two compounds remains an interesting question for further investigation. This report demonstrates the safe co-administration of two kinase inhibitors in an individual with two distinct

hematopoietic malignancies and represents an important precedent in the use of targeted molecular therapies.

Conflict of Interest

None declared.

Authorship

LKS: performed literature review, drafted manuscript, and generated figure. FMM: performed cytogenetic studies and assisted in editing of manuscript. AFT: was involved in clinical care of the patient. RSD: was involved in the clinical care of the patient and drafted and edited manuscript.

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