CONCOMITANT USE OF VENETOCLAX 100 MG AND KETOCONAZOLE TO TREAT CLL IN A PUBLIC CENTER IN BRAZIL

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INTRODUCTION

Venetoclax, a potent and selective B-cell lymphoma 2 (BCL-2) inhibitor, has demonstrated substantial efficacy as a monotherapy and in combination with other agents in the treatment of chronic lymphocytic leukemia (CLL). Its use has led to high response rates, durable remissions, and long survival, both in treatment-naive and relapsed/refractory CLL patients. However, the metabolism of venetoclax primarily relies on the cytochrome P450 enzyme CYP3A4, which can be influenced by concurrent administration of strong CYP3A4 inhibitors, including ketoconazole, itraconazole, clarithromycin, and ritonavir. These drugs have the potential to interact with venetoclax by inhibiting its metabolism resulting in elevated venetoclax plasma concentrations, increasing the risk of adverse events, particularly tumor lysis syndrome. Consequently, dose adjustments of venetoclax are necessary when coadministering with these inhibitors. Venetoclax availability in the public setting in Brazil is currently limited, with irregular donations being the only possible source. Therefore, we have made the decision to utilize the strong CYP3A4 inhibitor ketoconazole to save venetoclax tablets in an effort to maximize treatment opportunities for as many patients as possible.

OBJECTIVE

The objective of this analysis was to evaluate the efficacy and safety of the combination therapy of ketoconazole, low-dose venetoclax, and rituximab in the treatment of patients with chronic lymphocytic leukemia (CLL).

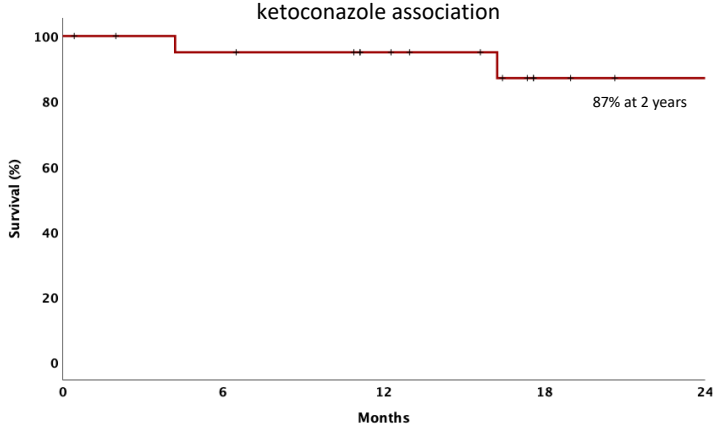
METHODS

Patients received venetoclax starting on day 22 of cycle 1, with a 5-week dose ramp-up (20 mg, 50 mg, 100 mg, and 200 mg). Subsequently, they received venetoclax 100 mg in combination with ketoconazole 200 mg daily until completion of cycle 12 (for patients in the first line of treatment) or cycle 24 (for patients in further treatment lines). Intravenous rituximab was also administered for six cycles, 375 mg/m2 in cycle 1 and 500 mg/m2 in cycles 2 to 6. All patients included in the analysis had received a minimum of 6 months of treatment at the time of data collection.

RESULTS

A total of 22 treatment regimens for 19 patients were included in this analysis. The median duration of venetoclax treatment was 12 months, ranging from 6 to 67 months. Seven patients (32%) received the treatment as a first-line therapy, 5 (23%) as a second-line therapy, 8 (36%) as a third-line therapy, and the remaining patients received it in further lines of treatment. The overall response rate was 100%, with 14 treatments leading to a complete response and 8 treatments to a partial response. Among the partial responders, 5 patients are still receiving treatment, and 3 patients completed six months of treatment and were referred to an allogeneic stem cell transplantation. The most common grade 3 or 4 adverse event observed was neutropenia, which occurred in 12 treatments. Notably, no cases of grade 2 or higher hepatic toxicity related to ketoconazole were reported. Additionally, there were no treatment-related deaths observed in the study. At a median follow-up of 19 months (range: 6-46), the median progression-free survival (PFS) has not been reached, and the PFS at 24 months was 87% (Figure 1). Three cases of disease progression occurred after 26, 30, and 39 months after the end of the treatment.

Figure 1. PFS at 24 months of patients who received venetoclax and ketoconazole association



All three patients were successfully retreated with the same treatment combination and achieved at least a partial response again. The median overall survival (OS) has not been reached, and the OS at 24 months was 95%. Three deaths were recorded during the study period: one patient died from acute myelogenous leukemia, one patient from a myocardial infarction, and one patient due to an unrelated intestinal bleeding.

CONCLUSION

Our data indicate that the combination of ketoconazole, low-dose venetoclax, and rituximab showed favorable tolerability and promising effectiveness in patients with CLL. This treatment approach could serve as a valuable alternative for patients in regions with restricted availability of targeted therapies. Further studies and larger-scale investigations are warranted to confirm these observations and validate the potential benefits of this combination regimen in the management of CLL in similar settings.

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