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Case Report

Ibrutinib in association with venetoclax for the treatment of mantle-cell lymphoma: a multicenter case series

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Abstract: Introduction: Mantle-cell lymphoma (MCL) with relapsed/refractory (R/R) disease after intensive chemotherapy have few effective treatment options. Ibrutinib showed a promising median progression-free survival (PFS) with manageable toxicity. The BCL2 inhibitor venetoclax showed encouraging results in R/R MCL patients and preclinical models suggest a potential synergistic effect of dual BTK and BCL2 inhibition. Ibrutinib in association with venetoclax was successfully investigated in a phase II trial. Case report: We have retrospectively analyzed 4 patients with R/R MCL receiving daily oral ibrutinib in association with venetoclax. All patients received oral ibrutinib 560 mg per day as monotherapy and subsequently added venetoclax with an initial dose of 50 mg per day, with weekly rump-up until a full dose of 400 mg per day until disease progression. All patients achieved a response, the CR rate was 50%. The aim was to perform an allogeneic SCT (allo-SCT). One patient experienced an early relapse and died because of PD. Allo-SCT was successfully performed in the other 3 patients; ibrutinib and venetoclax were discontinued before allo-SCT. One patient died because of transplant-related complications, while the other 2 cases are alive and in CR. No tumor lysis syndrome occurred. Discussion: Ibrutinib plus venetoclax represents a promising and feasible treatment option for R/R MCL patients outside clinical trials.

Keywords: Mantle-cell lymphoma, venetoclax, ibrutinib

Introduction

Mantle-cell lymphoma (MCL) is an aggressive non-Hodgkin lymphoma (NHL) subtype often characterized by poor prognosis despite high-dose chemotherapy [1]. Pleomorphic and blastoid variants and cases harboring TP53 disruptions are characterized by poor outcome despite novel agents and stem cell transplantation (SCT) [2].

The irreversible Bruton kinase (BTK) inhibitor ibrutinib showed a promising median progression-free survival (PFS) and overall survival (OS) with manageable toxicity, especially when administered as 2nd line therapy [3, 4]. In a long-term follow-up analysis, median PFS and OS were 12.5 and 26.7 months, respectively; unfortunately, patients with chemo-refractory disease and/or TP53 aberrations experienced a less favorable outcome and the authors suggest ibrutinib could be associated with other agents in this context [5]. The BCL2 inhibitor venetoclax was successfully investigated in relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL); because of BCL2 overexpression in MCL, there is a strong rationale to use venetoclax in R/R MCL cases [6, 7]. Treatment efficacy was firstly reported in a phase I study including many NHL subtypes, with an encouraging median PFS of 14 months for MCL cases [8]. Venetoclax resistance in MCL was predominantly associated with non-BCL2 gene mutations, further suggesting the need for combination therapy [9].

Table 1. Characteristics of patients, response to treatment and toxicity

Characteristic	Number of patients (%)
Age: median [range]	47 years [40-59]
Men	3/4 (75%)
Ann Arbor stage IV	4/4 (100%)
Elevated MIPI	3/4 (75%)
ECOG PS 0-1	4/4 (100%)
Elevated LDH	3/4 (75%)
Bone marrow involvement	4/4 (100%)
Blastoid or pleomorphic variant	3/4 (75%)
Ki67 >30%	4/4 (100%)
Chemorefractory to 1st line	4/4 (100%)
Chemorefractory to most recent therapy	4/4 (100%)
Previous therapy	
Rituximab	4/4 (100%)
High-dose cytarabine	4/4 (100%)
Anthracycline	4/4 (100%)
Bendamustine-cytarabine (BAC)	1/4 (25%)
Response to ibrutinib	
CR	1/4 (25%)
PR	2/4 (50%)
SD	1/4 (25%)
Response to ibrutinib plus venetoclax	
CR	2/4 (50%)
MRD-negative	1/4 (25%)
PR	2/4 (50%)
Toxicity	
Grade 3 neutropenia	1/4 (25%)
Grade 1-2 diarrhea	2/4 (50%)
Grade 1 skin rash	1/4 (25%)

Abbreviations: MIPI, mantle-cell lymphoma International Prognostic Index; PS, performance status; LDH, lactate dehydrogenase; CR, complete remission; PR, partial remission; SD, stable disease; MRD, minimal residual disease.

Ibrutinib in association with venetoclax was investigated for both previously untreated and R/R CLL patients; in a phase II study, this regimen was successfully administered to 24 MCL cases, with a better outcome than reported for ibrutinib or venetoclax monotherapy, including long-lasting MRD-negative CRs [10-12].

According to this background, the aim of the study is to investigate the efficacy and safety of this promising combination therapy in chemorefractory younger MCL patients outside clinical trials.

Case report

We have retrospectively analyzed 4 R/R MCL patients managed in 4 Italian Hematological Institutions, diagnosed between June 2017 and August 2018, receiving daily oral ibrutinib in association with venetoclax. As the use of venetoclax in MCL is off-label in Italy, access to the drug was obtained thanks to the 5% Italian Drug Agency (AIFA) Fund for innovative drugs. All procedures performed were in accordance with the ethical standards and were approved by the Institutional Review Board of single Institutions. All patients gave written informed consent in accordance with the Declaration of Helsinki. To reduce tumor-lysis syndrome (TLS) risk, all cases started ibrutinib single-agent 560 mg per day for at least 4 weeks and subsequently added venetoclax with the initial dose of 50 mg per day, with weekly ramp-up until a full dose of 400 mg per day, as previously published [12]. Treatment response was evaluated according to 2014 Lugano criteria, any adverse events were assessed according to the CTCAE criteria and descriptive statistics was used for patient's characteristics, as illustrated in **Table 1**.

All cases were younger (age at diagnosis was 40, 44, 50 and 59 years, respectively), had adverse prognostic factors and received cytarabine-based regimens as front-line therapy with curative intent but were chemo-refractory. Response to ibrutinib monotherapy was CR, partial response (PR) and stable disease (SD) in 1/4, 2/4 and 1/4 patients, respectively, with an ORR of 75%. After combination therapy, at week 16, all patients achieved a response, CR rate was 50% (2 cases, 1/2 was MRD-negative by flow cytometry). Furthermore, in 2/4 cases an improved response was reported compared to ibrutinib alone (from SD to PR and from PR to CR, 1 case each). No TLS occurred and overall toxicity was manageable, including grade 3 neutropenia (1 case, successfully managed with filgrastim), transient grade 1-2 diarrhea (2 cases, managed with anti-motility agents) and skin rash (1 case).

Due to younger age and good clinical conditions, the aim was to perform an allogeneic SCT

Table 2. Clinical results of ibrutinib in association with venetoclax

	Jain and colleagues	Hillmen and colleagues	Tam and colleagues	Current study
Patient population	CLL 1st line	CLL R/R	MCL R/R	MCL R/R
Number of patients	80	54	24	4
Regimen	Ibrutinib 420 mg once daily for 3 cycles, followed by venetoclax addition (ramp-up until 400 mg once daily), 24 cycles of combined therapy	Ibrutinib 420 mg once daily for 8 weeks, followed by venetoclax addition (ramp-up until 400 mg once daily), until PD or after 6 months of MRD-negative disease	Ibrutinib 560 mg once daily for 4 weeks, followed by venetoclax addition (ramp-up until 400 mg once daily), until PD	Ibrutinib 560 mg once daily for 4 weeks, followed by venetoclax addition (ramp-up until 400 mg once daily), until PD
ORR (%)	100% after 12 cycles	89% after 12 cycles	71% at week 16	100%
CR (%)	88% after 12 cycles	51% after 12 cycles	62% at week 16	50%
Grade 3-4 toxicity	Neutropenia 48%, thrombocytopenia 2%, atrial fibrillation and hypertension 10%	Infections 16.6%, neutropenia 62.9%, thrombocytopenia 25.9%, diarrhea 7.4%, hypertension 9.2%, atrial fibrillation and TLS 1.8%	Diarrhea 12%, neutropenia 33%, anemia 12%, thrombocytopenia 17%, atrial fibrillation and TLS 8%	Neutropenia 25%
Survival	1-y PFS 98%, 1-y OS 99%	1 progression, no deaths after a median follow-up of 21.1 months	18-months PFS 57%, 18-months OS 74%	1 progression, 1 death after allo-SCT, 2/4 cases alive in CR 1 year after allo-SCT

Abbreviations: CLL, chronic lymphocytic leukemia; MCL, mantle-cell lymphoma; R/R, relapsed/refractory; PD, progressive disease; MRD, minimal residual disease; ORR, overall response rate; CR, complete response; TLS, tumor lysis syndrome; PFS, progression-free survival; OS, overall survival; SCT, stem cell transplantation.

(allo-SCT) in all cases. Unfortunately, 1 patient experienced an early relapse and died because of PD. This case was refractory to high-dose cytarabine-containing regimens and to cytarabine in association with bendamustine, presented with a blastoid variant of MCL, advanced-stage disease and high Ki-67 level, all characteristics associated with dismal prognosis. A mutation analysis was not available in daily clinical practice, but we can speculate this case could have acquired genetic alterations associated with primary resistance or relapsed disease after an initial response, such as mutations in components of the SWI-SNF chromatin-remodeling complex, that were linked to a transcriptional upregulation of Bcl-xL [13].

Remarkably, allo-SCT as consolidation was successfully performed in the other 3 patients; pre-transplant disease restaging showed PR and CR in 1 and 2 cases, respectively. Ibrutinib and venetoclax were discontinued before allo-SCT. One patient died following transplant-related complications after 3 months, while the other 2 cases are alive and in CR at last follow-up 12 months after allo-SCT.

Discussion

In our experience in a small cohort we observe that ibrutinib and venetoclax can be administered in association in daily clinical practice, with high efficacy, including long-lasting CR and manageable toxicity in R/R MCL patients with adverse prognostic factors, such as TP53 aberrations, high MIPI score, high Ki-67 level and blastoid or pleomorphic variants.

Despite promising results as a single-agent, primary or acquired ibrutinib resistance has been observed and patients with chemo-refractory disease could achieve a less favorable outcome, further suggesting the need of a combination therapy with drugs with a different target such as venetoclax. As showed in **Table 2**, ibrutinib in association with venetoclax was investigated for both previously untreated and R/R CLL and MCL patients, including cases with 17p deletion, with high CR rate and many cases achieving an undetectable MRD [10-12]. In a phase II study involving 80 older and/or high-risk untreated CLL cases (characterized by TP53 disruptions and/or 11q deletion and/or unmutated IGHV genes), CR rate was 88% after 12 cycles of combined therapy (61% were MRD-negative). Remarkably, 1-y estimated PFS was 98% and treatment response improved over time across all subgroups, including patients with TP53 mutations [10]. The CLARITY trial enrolled 54 R/R CLL patients, most of them relapsed after fludarabine-cyclophosphamide-rituximab and bendamustine-rituximab. After 12 months of combined therapy, ORR, CR rate and MRD-negative rate were 89%, 51% and 36%, respectively; after a median follow-up of 21.1 months, all evaluable patients were alive [11].

Tam and colleagues enrolled 24 MCL patients in a phase II trial, most of them harboring TP53 aberrations and/or high MIPI score [12]. CR rate was 62% at week 16 (67% of CRs were MRD-negative) and in 78% of patients who achieved a response it was ongoing at 15 months [12]. As our patients are similar to those described in the trial, we confirm the possibility to achieve a long-lasting CR with this combination regimen. Furthermore, we suggest venetoclax plus ibrutinib could be a useful bridge to allo-SCT in eligible patients achieving at least a PR. TLS could represent an important adverse event, but it is manageable with adequate dose ramp-up, fluid intake and anti-hyperuricaemic drugs [14]. To our knowledge, our experience represents the first report of efficacy and feasibility of ibrutinib in association with venetoclax in MCL outside clinical trials. It could represent a useful treatment regimen for high-risk R/R MCL patients and a possible bridge to allo-SCT, that remains the only potentially curative option.

Disclosure of conflict of interest

None.

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