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Case Series
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Case Series of Safety of *BCL2* and *IDH* Inhibition Combination for Myeloid Leukemia

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Abstract

The incidence rate of leukemia was 13.8% between 2011 to 2015 and the death rate was 6.5% between 2012 to 2016. The data shows that the death rate was almost half of the incidence and need for newer therapies to treat leukemia. Acute myeloid leukemia is characterized by rapid growth of myeloid lineage cells in the bone marrow and appearance of blasts in peripheral blood. The mainstay of treatment is chemotherapy and sometimes given with targeted drug therapy. Targeted drugs work differently compared to standard chemotherapy and when used individually for treatment has given encouraging results. We report a case series of three patients treated at our center for relapsed AML with *IDH* inhibitor and *BCL-2* inhibitor combination for more than 2 months and attained morphological leukemia free state and cytopenia.

Introduction

Acute Myeloid Leukemia (AML) is a malignant disorder of hemopoietic stem cells characterized by clonal expansion of abnormally differentiated blasts of myeloid lineage [1]. With the development of methodologies of large scale sequencing, new genetic mutations associated with AML have been identified, offering new opportunities for therapy [2]. Recent discoveries have highlighted an important role of dysregulated epigenetic mechanisms in the pathogenesis of the disease [3]. Current agents that affect epigenetic are the DNA methyltransferase inhibitors, azacitidine and decitabine and both drugs have activity against AML [4].

Additionally, various novel agents targeting molecular pathway abnormalities have demonstrated clinical activity, either as single agents (e.g. Isocitrate Dehydrogenase (*IDH*) inhibitors or *BCL-2* inhibitors) or in combination with standard therapy at diagnosis or in salvage [5]. *IDH* inhibitors such as enasidenib (*IDH*2 inhibitor) and ivosidenib (*IDH1* inhibitor) as well as *BCL-2* inhibitor venetoclax have been approved by FDA for treatment of AML [6-8]. Responses are very encouraging, though cure still not achieved, thus prompting interest in novel combinations. These studies are ongoing and we support their completion and eagerly await their conclusions, however current patients and physicians need guidance on combinations that may be tried in the interim. Thus, we report a case series of three sequentially treated patients treated at our center for relapsed AML with *IDH* and *BCL-2* inhibitor combination. This retrospective review was approved by our local IRB. Electronic medical records were reviewed for response, safety, and toxicity of the combination (Table 1).

Case Series

Case 1

The first patient is 63 years of age with secondary AML and received standard '7+3' induction for secondary AML with multiple molecular abnormalities including *IDH1* and *IDH2* abnormalities. He had progression within 2 weeks and thus was given decitabine 20 mg/m^2 for 10 days a month and enasidenib 100 mg daily. The patient achieved a short lasting hematologic remission with a bone marrow biopsy performed at 3 months due to worsening counts confirming progression. Venetoclax 400 mg daily was added to the current doublet regimen. Dose reduction was not necessary as he was not on any antifungal drugs. The patient received 2 cycles of this triplet over 2 months which resulted in a morphologic leukemia Free State and negative molecular next generation sequence result. He is currently early post allogeneic transplantation with successful engraftment and remission continues.

Case 2

The second patient is a 68 years of age with secondary leukemia arising from CMML. He received decitabine based therapy in combination with other phase 1 study agents, deriving a morphologic

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Table 1: Electronic medical records were reviewed for response, safety, and toxicity of the combination.

Pt	Initial Treatment/ response	Muttation	Cytogenetics	IDH inhibitor used and dose	Venetoclax dose and frequency	HMA dose and frequency	Duration of response to combination	Toxicity	Response
1	7+3 induction therapy/2 weeks	IDH1 IDH2	Trisomy 13	Enasidenib 100 mg daily	Venetoclax 400 mg daily	Deciatbine 20 mg/m^2 10 days once a month	3+ months	Leukopenia	MLFS
2	Decitabine+phase 1 agent/14 months	IDH2	Normal	Enasidenib 100 mg daily	Venetoclax 200 mg d 1 to 14	Azacitidine 75 mg/m^2 for 5 days/month	6+ months	Thrombocytopenia	CRi
3	Decitabine 20 mg/m^2 5 days a month/enasidenib 100 mg daily × 6 months	IDH2	Normal	Enasidenib 100 mg daily	Venetoclax 200 mg d 1 to 14	None	2 months	Thrombocytopenia	MLFS

remission lasting 14 months and proceeded to additional clinical trials with 8 months of stable disease. At failure of this, single agent enasidenib 100 mg daily was initiated and the patient had stable disease but persistent thrombocytopenic for 10 months. With disease progression, venetoclax 400 mg daily was added and the patient was tolerating well for 20 days but continued to have thrombocytopenia requiring dose reduction to 200 mg daily. Leukocytosis was noted after 1 month (unclear if differentiation syndrome) and azacitidine 75 mg/m^2 daily for 5 days monthly was added to the daily enasidenib and venetoclax for 14 days per month maintained at the same dose. A morphologic remission was documented at 3 months and he remains so at 5 months of triplet therapy.

Case 3

The third patient is 73 years old and received decitabine 20 mg/m^2 5 days monthly as single agent for initial AML therapy and with tolerance the enasidenib 100 mg daily was added with cycle 2 and the patient attained CRi at 3 months, though relapsed 9 months after the initiation of the doublet. Venetoclax 200 mg daily was started as he was on posaconazole as well. The patient experienced pancytopenia within 2 weeks and both drugs were held for 1 week. Enasidenib was restarted and then venetoclax 200 mg was added for days 1 to 14 per cycle. Patient has been on the combination for 2 months with MLFS, though transfusion dependent still.

The efficacy of single agent *IDH* and *BCL-2* inhibitors has been proven for AML treatment, but this is the first report to our knowledge of their combination. We await the results of the larger phase 1 to 2 combination studies, however current patients in need of alternatives may benefit from this early insight to tolerance. Enasidenib and venetoclax when used together or with a hypomethylator can effectively decrease hematopoiesis even in patients with rapidly increasing leukocytosis. Given the significant cytopenia our initial patients encountered daily *IDH* inhibition with only 2 weeks of *BCL2* inhibition is a reasonable starting point for patients in need.

Conflict of Interests

Dr. Rizzieri has served as a consultant and receives research support from Agios Pharmaceuticals and Celgene.

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