

The DREPANO COVID-19 collaborative group is listed in supplemental file (Appendix S1)

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REFERENCES

1. Singh A, Brandow AM, Panepinto JA. COVID-19 in individuals with sickle cell disease/trait compared with other Black individuals. *Blood Adv.* 2021;5:1915-1921.
2. Arlet JB, de Luna G, Khimoud D, et al. Prognosis of patients with sickle cell disease and COVID-19: a French experience. *Lancet Haematol.* 2020;7:e632-e634.
3. Panepinto JA, Brandow A, Mucalo L, et al. Coronavirus disease among persons with sickle cell disease, United States, March 20–May 21, 2020. *Emerg Infect Dis.* 2020;26:2473-2476.
4. Telfer P, De la Fuente J, Sohail M, et al. Real-time national survey of COVID-19 in hemoglobinopathy and rare inherited anemia patients. *Haematologica.* 2020;105:2651-2654.
5. Elenga N, Celicourt D, Muanza B, et al. Dengue in hospitalized children with sickle cell disease: a retrospective cohort study in the French departments of America. *J Infect Public Health.* 2020;13:186-192.
6. Rankine-Mullings A, Reid ME, Moo Sang M, Richards-Dawson MA, Knight-Madden JM. A retrospective analysis of the significance of haemoglobin SS and SC in disease outcome in patients with sickle cell disease and dengue fever. *EBioMedicine.* 2015;2:937-941.
7. Renoux C, Romana M, Joly P, et al. Effect of age on blood rheology in sickle cell anaemia and sickle cell Haemoglobin C disease: a cross-sectional study. *PLoS One.* 2016;11:e0158182.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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Venetoclax combined with FLAG-based chemotherapy induces an early and deep response in mixed-phenotype-acute leukemia

To the Editor:

Mixed-phenotype acute leukemia (MPAL) is a rare and heterogeneous group of malignant diseases, accounting for 2%–5% of acute leukemias. They are classified according to the European Group for Immunological Characterization of Leukemias, and the World Health

Organization (WHO) as leukemia that expresses antigens of more than one lineage, myeloid (My), B or T lymphoid lineage, to such a degree that it is not possible to assign leukemia to a single lineage with certainty.¹ The genetic aberrations that drive MPAL remain largely unknown, with the exception of a small subset of MPALs harboring *BCR-ABL1* or *KMT2A* rearrangements. The diversity of phenotypes observed in MPAL may result from acquisition of mutations in a multipotent progenitor cell that primes leukemia cell for lineage promiscuity.² MPAL are high-risk diseases with a poor overall survival. In multivariate analysis, minimal residual disease (MRD) analysis therapy represents, as for other subtypes of acute leukemia, a major prognosis factor.

The choice of the induction chemotherapy regimen is not consensual due to the phenotypic heterogeneity of the disease. Most of the clinical data regarding response to treatment come from retrospective studies and case reports. The most widely used regimen is either acute myeloid leukemia (AML) or preferably acute lymphoid leukemia-based therapy.³ However, it can lead to clonal expansion of blasts, which may resist the initial lineage-based chemotherapy.

FLAG-IDA induction including fludarabine (30 mg/m² D2–D6), cytarabine (2 g/m² D2–D6), idarubicin (6 mg/m² D2–D4), and filgrastim 5 µg/kg is an effective and well-tolerated induction chemotherapy, which provides high complete remission rates in newly diagnosed (ND) and relapsed/refractory (R/R) AML. Venetoclax (VEN) is a BCL-2 inhibitor, which has been approved in combination with hypomethylating agents (HA) or low-dose cytarabine for the treatment of ND AML in patients 75 years of age or older who are unfit for intensive induction chemotherapy. Venetoclax combined with HA improved patient-overall and event-free survival.⁴ Previous studies reported in MPAL the efficacy of VEN in combination with HA.⁵ For younger and fit patients with ND or R/R AML, adding VEN to FLAG-IDA recently showed impressive results,⁶ suggesting a synergistic effect of VEN with intensive chemotherapy. MRD-negative composite CR was achieved in 96% of ND and 69% of R/R AML.

Here we present our findings in three patients with MPAL, who were treated with VEN combined with FLAG with or without idarubicin. We performed a retrospective review of single-center case series.

After patient informed consent, we extracted clinical, biological data from clinical records and analyzed flow cytometry data, to define patients fulfilling the criteria of MPAL according to WHO classification;¹ and significantly expressing BCL-2 (Figure 1). MPAL with t(9;22) (q34;q11.2) were excluded because other targeted treatments are available (tyrosine kinase inhibitors).

Three consecutive patients with MPAL were included between July 2020 and May 2021. Their median age was 43.9 years (19.8–53.3). One patient was in second relapse post-allogeneic transplant, and two were ND. Flow cytometry and immunohistochemistry analyses showed that the MPAL immunophenotype of the first patient was compatible with the rare B/T MPAL with positivity for CD19, CD7, CD33, cCD79a, cCD3, and TDT. MPO was negative. The second MPAL was a T/Myeloid MPAL

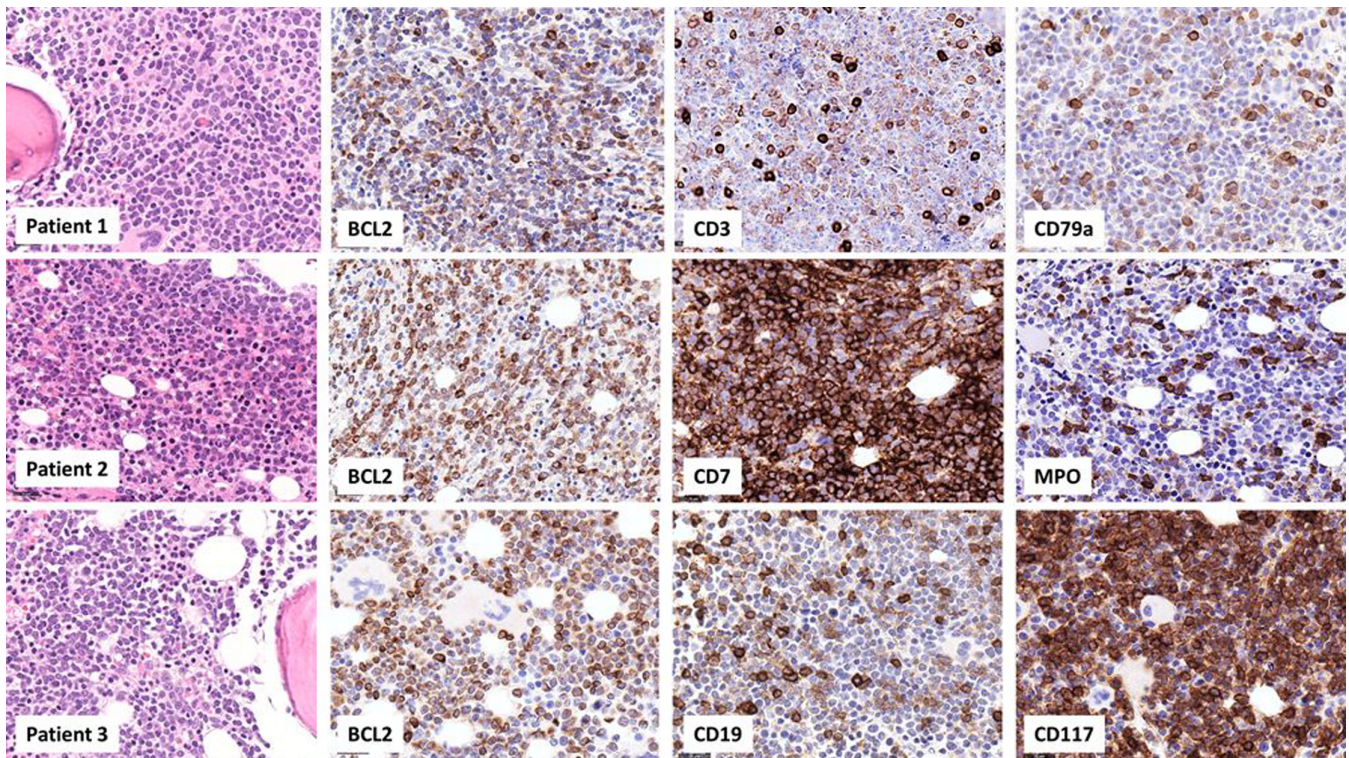


FIGURE 1 Bone marrow core biopsy section of the three patients (patient 1: T/B MPAL; patient 2: T/My MPAL; patient 3: B/My MPAL) Hematoxylin & Eosin, $\times 20$ optical magnification. Immunohistochemical stains for bcl2, CD3, CD79a, CD7, myeloperoxidase (MPO), CD19, and CD117

coexpressing CD117, CD34, CD13, partially CD33, CD38, CD3, CD2, CD5, CD7, cytoplasmic CD3 (cCD3), MPO, and TDT antigens. The immunophenotype of the third MPAL was that of a B/Myeloid MPAL expressing CD19, cCD79a, CD117, CD34, CD13, CD7, CD4, MPO, and TDT. BCL-2 was highly expressed in all patients (by $>90\%$ of CD34⁺ cells). The B/T MPAL had a complex karyotype revealed by DNA microarray analysis. The karyotype of the T/myeloid MPAL was normal while it was hyperdiploid in the B/Myeloid with an additional trisomy 3. Multiplex ligation-dependent probe amplification identified the rearrangement of PICALM-MLLT10 in the B/T MPAL that exhibited also monoclonal IgH and TCR gamma gene rearrangements. Next-generation sequencing detected DNMT3A and NOTCH1 mutations in the T/Myeloid MPAL, a monoclonal TCR delta rearrangement was present. The B/Myeloid MPAL had RUNX1 and BCOR mutations.

Patients with B/Myeloid and T/Myeloid MPAL received two induction cycles of FLAG-IDA, combined with VEN (400 mg/day for 10 days). The patient with B/T MPAL, in relapse post-transplant, received one cycle of FLAG combined with VEN and a single dose of gemtuzumab ozogamycin (FLAG-GO-VEN) on D3, given the high levels of CD33 expression.

In our case series, FLAG-VEN therapy was well-tolerated. The median duration for neutrophil ($>500/\text{mm}^3$) and platelet recovery ($>100\,000/\text{mm}^3$) were 16 days (14–26) and 32 days (26–34), respectively. Aplasia was complicated by four episodes of febrile neutropenia in three patients. The patient treated with FLAG-GO-VEN had a grade 2 cytolysis, which evolved favorably within 72 h.

After the first induction cycle, all patients had undetectable MRD by flow cytometry and 2 by IgH/TCR rearrangements with a sensitivity $\leq 10^{-4}$. After a median follow-up of 7.1 months (5–14), all patients are in complete molecular remission. Median progression-free survival and OS have not yet been reached. No patient died during the follow-up period.

After two cycles of FLAG-VEN, all three patients successfully underwent allogeneic stem cell transplantation.

Venetoclax, in combination with FLAG-VEN chemotherapy, seems to be an effective and well-tolerated treatment for MPAL. Furthermore, it appears to induce a deep and early complete molecular response in both frontline and relapsed disease, including rare subtypes such as T/B MPAL. Indeed, rapid response to treatment is a major challenge in this poor prognosis disease, especially as a bridge to allogeneic stem cell transplantation, which remains the only curative treatment. These encouraging results need to be confirmed in further prospective clinical trials.

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CONFLICT OF INTEREST

Authors declare that they have no conflict of interest.




AUTHOR CONTRIBUTION

Amandine Ségot and Olivier Spertini designed the study; Amandine Ségot and Olivier Spertini wrote the manuscript; Amandine Ségot,

Olivier Spertini, Sabine Blum treated the patient, Amandine Ségot, Olivier Spertini, and Grégoire Stalder collected and analyzed the data; Laurence de Leval provided the pathological analysis; Jacqueline Schoumans provided the oncogenomics analysis; Françoise Solly provided the molecular biology analysis; Valentin Basset, Françoise Solly, and Olivier Spertini reviewed the flow cytometry data; and all authors reviewed and edited the paper.

INFORMED CONSENT

Signed informed consents were obtained from the patients included in this work.

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REFERENCES

- Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016;127(20):2391-2405.
- Alexander TB, Gu Z, Iacobucci I, et al. The genetic basis and cell of origin of mixed phenotype acute leukaemia. *Nature*. 2018;562(7727):373-379.
- Reid JH, Perissinotti AJ, Benitez LL, et al. Hybrid chemotherapy regimen (FLAG-IDA-vincristine-prednisone) for acute leukemia with mixed-phenotype blasts. *Leuk Res*. 2021;103:106539.
- DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and Venetoclax in previously untreated acute myeloid leukemia. *N Engl J Med*. 2020;383(7):617-629.
- Wu D, Chen W, Chen Z, Li Q. Venetoclax combined with hypomethylating agents for treatment-Naïve B/myeloid mixed phenotype acute leukemia. *Case Rep Hematol*. 2021;2021:6661109.
- DiNardo CD, Lachowicz CA, Takahashi K, et al. Venetoclax combined with FLAG-IDA induction and consolidation in newly diagnosed and relapsed or refractory acute myeloid leukemia. *J Clin Oncol*. 2021;9(25):2768-2778.

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Patient-focused inquiry on hydroxyurea therapy adherence and reasons for discontinuation in adults with sickle cell disease

To the Editor:

For decades, Hydroxyurea (HU) was the only Food and Drug Administration (FDA) approved medication for treating adults with sickle cell disease (SCD) with demonstrated efficacy in reducing the frequency of painful crises, hospitalizations, and blood transfusions.¹⁻⁴ While recently approved agents have been found to offer reductions in the frequency of painful crises and hospitalizations (L-glutamine), in the number of painful crises (crizanlizumab), and in anemia and hemolysis (Voxelotor), HU remains the first-line agent for individuals with SCD over the age of 2 years.⁵⁻⁷ Despite its proven utility, many patients are either not prescribed it or are not taking the medication.^{8,9} Few studies exist to date that evaluates reasons behind this phenomenon from the patient's perspective.

Between October 2017 and February 2019, patients with SCD seen at the Montefiore Medical Center's Sickle Cell Center for Adults completed a survey instrument that collected demographic information, disease course, and past and current treatments. Surveys were offered in English and Spanish. Data from 224 adults were available for analysis. Additional information was collected from the electronic medical record (EMR), and survey results were verified using the EMR. This study was approved by Montefiore Institutional Review Board (IRB) as exempt from consent.

Patient demographics for the 224 patients surveyed are presented in Table S1. Of the 224 patients, 57 had "mild" disease genotypes (HbSC or Hb Beta Thal +) and 167 had "severe" genotype (HbSS or HbS Beta/0 thal). Overall, 77.2% of patients surveyed had ever been prescribed HU. Of those who had ever been prescribed HU, 65.3% reported taking it at the time of this study. Among patients with "mild" SCD genotypes, 42.1% reported ever having been prescribed HU, with 50% of these patients taking it at the time of this study. For those with severe disease genotypes, 91.0% had ever been prescribed HU, 68.4% of whom reported taking it at the time of this study.

Of 146 patients who were currently taking the medication, patients reported variable duration of HU use: 8.1% had taken HU for