

LETTER TO THE EDITOR

Salvage monotherapy with venetoclax after failure from a single course of standard induction chemotherapy for acute myeloid leukaemia

Primary refractory disease for acute myeloid leukaemia (AML) is defined by the 2017 European LeukemiaNet (ELN) as the persistence of $\geq 5\%$ blasts in bone marrow after two cycles of intensive chemotherapy or one cycle of high-dose cytarabine and can occur in 10%–40% of treated patients.^{1,2} The risk of failure after induction therapy containing daunorubicin and cytarabine (“3+7”) increases with the prognostic category of the AML and is associated with a poorer outcome.³ Classically, when facing a refractory situation, most centres proceed to another cycle of induction chemotherapy with an anthracycline-based regimen to achieve remission. Even though this strategy has proven effective, it significantly increases toxicity and the length of hospital stay. Given the fact that allogeneic stem cell transplantation is statistically the preferred consolidation therapy for fit patients, other less toxic strategies are of particular interest for more vulnerable patients. Over recent years, venetoclax has become a game-changing drug in the management of AML. Encouraging results have led to its combination with an induction regimen such as intensive chemotherapy, hypomethylating agents and low-dose cytarabine.^{4,5} Furthermore, the use of azacitidine plus venetoclax in the relapsed/refractory setting has been demonstrated to be an efficient bridging therapy to allogeneic stem cell transplantation.⁶ Other venetoclax combinations have also become increasingly used with promising results.^{7,8} However, to our knowledge, salvage therapy based on a short course of venetoclax alone following standard induction therapy has never been reported.

Here, we describe the cases of four patients who were refractory to a single course of conventional induction therapy (“3+7”) for AML and for which salvage therapy with venetoclax monotherapy was used. We proposed this treatment to lessen toxicity given patient age and frailty. Among our patients and according to ELN 2022 guidelines,⁹ two had adverse prognosis AML, one intermediate prognosis and one favourable prognosis. Clinical details, treatment and outcome of the patients are summarised in Table 1 and Figure 1 (see also Data S1). Both patients with adverse prognosis AML evolved from myelodysplastic syndrome and had grade IV thrombocytopenia at diagnosis. Mean age of all patients was 65 (range: 54–76) years. Three patients were treated with conventional “3+7” induction therapy, while one received cytarabine alone due to

heart failure contraindicating anthracycline use (patient #4). After determination of blast persistence on day 21 bone marrow aspirate examination, all patients received salvage therapy with venetoclax 400 mg/day (100 mg/day if concomitant azole use) for 7 days. At day 28, bone marrow aspirate examination was repeated and showed morphologic leukaemia-free state in all patients. The two adverse prognosis patients as well as the patient with a favourable prognosis had incomplete haematological recovery. The mean time in aplasia, defined by an absolute neutrophil count $< 500/\mu\text{L}$, was 28 days. After venetoclax initiation, the mean time to neutrophils recovery ($> 1000/\mu\text{L}$) and platelets recovery ($> 100\,000/\mu\text{L}$) was 12 and 20 days respectively. Two patients were still in aplasia at the time of venetoclax termination and benefitted from granulocyte-colony stimulating factor support after day 28 to allow faster recovery. No specific infectious complications were noted after the short venetoclax course. Consolidation therapy was evaluated according to international guidelines and individualised. Two patients (patients #1 and #3) underwent allogeneic stem cell transplant, one (patient #2) benefitted from a combination of azacitidine and venetoclax and the last (patient #4) received intermediate-dose cytarabine.

This strategy with venetoclax appears to limit the toxicity of new exposure to chemotherapy while achieving blast clearance (for details, see Data S1). Classically, in fit patients with a chemosensitive AML phenotype, reinduction therapy is generally accepted as the gold standard. The main difficulty of such treatment involves toxic and infectious complications. Indeed, the use of higher anthracycline doses leading to increased cardiac toxicity or severe infection caused by prolonged aplasia can jeopardise efficient consolidation treatment such as allogeneic stem cell transplantation with significant transplant-related mortality. Venetoclax is known for its potent antineoplastic properties, which might provide a less toxic and efficient salvage therapy that would question optimal management in refractory patients. A less toxic treatment leading to complete remission would benefit patients by preserving transplant candidacy. Although long-term efficacy with respect to measurable residual disease negativity might be questioned for a short venetoclax course compared with a standard reinduction regimen, it can be inferred from the established efficacy of the azacitidine plus

TABLE 1 Clinical details of patients treated with venetoclax.

Variable	Patient #1	Patient #2	Patient #3	Patient #4
Patient characteristics				
Age (years)/gender	68/M	76/M	62/M	54/M
AML prognosis category ^a	Adverse	Adverse	Intermediate	Favourable
AML secondary to MDS	Yes	Yes (MDS/MPN syndrome)	No	No
Karyotype	46,XY	46,XY, pseudoploid, del7p	46,XY, del20q	46,XY
NGS mutations	<i>NPM1</i> , <i>SRSF2</i> , <i>ASXL1</i> , <i>TET2</i> , <i>CBL</i>	<i>NRAS</i> , <i>RUNX1</i> , <i>CEBPA non-bZIP</i> , <i>ASXL1</i> , <i>TET2</i> , <i>ETV6</i> , <i>EZH2</i>	No mutations	<i>NPM1</i> , <i>IDH1</i> , <i>NRAS</i>
Haemoglobin at diagnosis (g/dL)	10.6	10.6	11.3	9.8
Platelet count at diagnosis (per μ L)	23 000	28 000	107 000	151 000
Neutrophil count at diagnosis (per μ L)	5535	57 512	1022	852
Bone marrow blasts at diagnosis (%)	83	33	45	65
Induction therapy and outcome				
Induction chemotherapy	Idarubicin 12 mg/m ² for 3 days + cytarabine 200 mg/m ² for 7 days	Daunorubicin 60 mg/m ² for 3 days + cytarabine 200 mg/m ² for 7 days	Idarubicin 12 mg/m ² for 3 days + cytarabine 200 mg/m ² for 7 days	Cytarabine 200 mg/m ² for 7 days ^b
Bone marrow blasts at day 21 of IC (%)	60	9	10	8
MRD by flow cytometry at day 21 (%) ^c	30	7.5	10	10
Aplasia duration following IC (days)	31	21	18	41
Venetoclax therapy and outcome				
Venetoclax dose (mg/day)	400	400	400	400
Aplasia duration following venetoclax initiation (days)	12	0	2	19
Bone marrow blasts at day 28 of IC (%)	0	1	0	0
MRD by flow cytometry at day 28 (%) ^c	Negative	1.5	0.01	0.01
Consolidation therapy and outcome				
Consolidation therapy after venetoclax	Allo-SCT	Azacitidine + venetoclax	Allo-SCT	IDAC
Post-consolidation response	CR _{MRD-}	CR _i	CR _{MRD-}	CR _{MRD-}

Abbreviations: Allo-SCT, allogeneic stem cell transplantation; AML, acute myeloid leukaemia; CR_i, complete remission with incomplete count recovery; CR_{MRD-}, complete remission with no measurable residual disease; IC, induction chemotherapy; IDAC, intermediate-dose cytarabine; M, male; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; MRD, measurable residual disease; NGS, next-generation sequencing.

^aAccording to 2022 European LeukemiaNet criteria.⁹

^bNo anthracycline due to heart failure.

^cSensitivity 0.01%.

venetoclax combination as a bridging strategy to allogeneic stem cell transplantation.¹⁰ Furthermore, the reduced aplastic period following venetoclax treatment compared with re-induction theoretically decreases the risk of severe infection. The timing of venetoclax introduction also needs to be discussed. Two of our patients experienced severe and prolonged thrombocytopenia that could presumably have been secondary to bone marrow toxicity induced by venetoclax on the

early stem cell recovery process. However, both of these AML patients had developed from myelodysplastic syndrome with pre-existing thrombocytopenia, which precludes us from making a conclusion about the responsibility of venetoclax. Nevertheless, the optimal timing of venetoclax introduction still needs to be established. Similarly, the timing of the established day 21 bone marrow examination should be questioned as three of our patients showed an incomplete but

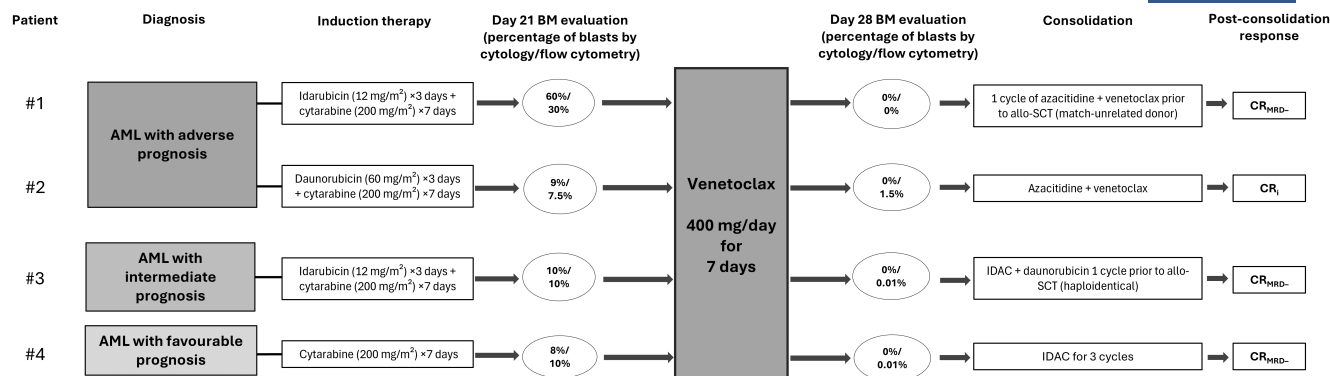


FIGURE 1 Timeline of patients' treatments and responses. AML, acute myeloid leukaemia; Allo-SCT, allogeneic stem cell transplantation; BM, bone marrow; CR_i, complete remission with incomplete hematological recovery; IDAC, intermediate-dose cytarabine; MRD, minimal residual disease.

significant decrease in blasts at that time. As retrospective studies have shown,^{11,12} some patients can still achieve remission at day 28 without the need for a second course of intensive chemotherapy. Adverse cytogenetics and persistence of blasts in bone marrow aspirate are, however, predictive of the need for retreatment. Of course, we are clearly limited in demonstrating the role of venetoclax in blast clearance given the low number of patients in our cohort.

In conclusion, we describe a case series of four patients treated with venetoclax monotherapy as a salvage regimen for refractory AML following a single course of standard induction chemotherapy. We believe that this strategy could be a valuable option by alleviating general toxicity and infectious risk compared with intensive reinduction chemotherapy, especially in a pre-allogeneic stem cell transplantation setting.

AUTHOR CONTRIBUTIONS

P-YS and FD wrote the manuscript with support from WB, EC and CG. P-YS collected all data. AS, MA, CD, HV, WB, GC, JDev, JDep, BD, FD and MP reviewed the results and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

No conflicts of interest are declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

ETHICS APPROVAL STATEMENT

This study received approval from our institutional review board.

PATIENT CONSENT STATEMENT

Written informed consent was obtained from the patients for publication of the details of their medical case and are available if required.

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