Intensive induction therapy with FLAG-idarubicin-venetoclax for fit older high-risk patients with acute myeloid leukemia

Low-intensity chemotherapy combined with venetoclax (LIC-VEN) has become the standard of care for older unfit patients with acute myeloid leukemia (AML). Recently, the treatment with LIC-VEN was proposed as an acceptable alternative to intensive chemotherapy also for fit, older patients,[1,2] achieving similar efficacy but with less toxicity. However, high treatment failure rates with LIC+VEN were reported in AML with an adverse-risk karyotype and in AML preceded by myeloproliferative disease or evolving after hypomethylating agent failure.[3-5] More recently, *RAS* and *TP53* mutations were identified as adverse prognostic factors for remission induction and survival in patients with AML treated with LIC-VEN.[6]

The treatment with fludarabine, cytarabine, granulocyte-colony stimulating factor (G-CSF), and idarubicin combined with venetoclax (FLAG-Ida-ven) has gained popularity in recent years for both newly diagnosed (N/D) and relapsed/refractory (R/R) AML. In the seminal phase Ib/II study by DiNardo *et al.*, composite complete remission (CRc) rates exceeded 60% for all subgroups[7] (CRc=complete remission [CR] + CR with incomplete count recovery [CRi] + morphological leukemia-free state [MLFS]). Moreover, most patients transitioned to an allogeneic stem cell transplantation (alloSCT) at first remission (CR1), with a 3-year overall survival for N/D and R/R cohorts of 66% and 32%, respectively.[8] Yet, these cohorts predominantly included younger patients; only 15% of patients were over 60 years of age. Subsequent studies confirmed the regimen's capacity to induce high remission rates, but consistently among younger adults,[9,10] thus not representing the majority of patients with AML who are diagnosed at a median age of 70 years.

The aim of this study was to evaluate the real-world experience of using FLAG-Ida-ven in consecutive patients aged 65 years or older with N/D and R/R AML, all treated as intent-to-transplant at the earliest feasible time point in a single tertiary-care center in Israel. All the procedures involved in this study were in accordance with the ethical standards of the Institutional Review Board of the Rambam Health Care Campus (Approval number RMB-0211-25) and with the 1964 Declaration of Helsinki and its later amendments.

Since June 2021, FLAG-Ida-ven has become the standard regimen for fit, high-risk AML patients at the Rambam Health Care Campus (Haifa, Israel). During the 4-year period between June 2021 and May 2025, 110 patients were treated with this regimen. All patients received fludarabine at a dose of 30 mg/m^2 for five days, and 14 days of 100 mg venetoclax. Cytarabine was administered at a dose of 1 g/m^2 for five days, given over 4 hours. The cumulative dose

Table 1. Patient characteristics.

Characteristics	N/D cohort N=14	R/R cohort N=20
Age range, years (median)	65-76 (70)	65-77 (71)
Disease, N		
AML	11	16
ALL	0	1
Ambiguous lineage leukemia, N	3	3
Leukemia ontogeny, N		
Therapy-related	5	4
Prior MDS	4	5
Prior MPN	5	3
de novo leukemia	3	9
ELN 2022 risk group, N		
Favorable	1	2
Intermediate	1	3
Adverse	12	15
Prior alloSCT, N	2	1
Prior HMA treatment, N	2	9
Prior venetoclax treatment, N	0	10
Prior anthracycline treatment, N	0	10
Idarubicin dose, N		
24 mg/m^2	9	9
16 mg/m^2	4	6
12 mg/m^2	1	5
Median days of platelets, <50x10^9/L, N	24.5	19
Median days of ANC, <500/μL, N	22	22
Median days in hospital, N	24.5	31
Response to treatment, N		
CR+CRi	7	5
MLFS	4	7
Refractory	2	6
Death before evaluation	1	2
MRD-negativity	8	7
Proceeded to alloSCT	12	9
Median N of days until alloSCT	53	42

ALL: acute lymphoblastic leukemia; alloSCT: allogeneic stem cell transplantation; AML: acute myeloid leukemia; ANC: absolute neutrophil count; CR+CRi: complete remission + complete remission with incomplete count recovery; ELN: European LeukemiaNet; HMA: hypomethylating agent; MDS: myelodysplastic syndrome; MLFS: morphological leukemia-free state; MPN: myeloproliferative neoplasms; MRD: minimal residual disease; N: number; N/D: newly diagnosed; R/R: relapsed / refractory.

of idarubicin was 12-24 mg/m^2, divided into 2-3 days, and this was decided for each patient based on fitness, prior therapies and cardiac status. All patients received prophylaxis with trimethoprim / sulfamethoxazole, quinolones, aciclovir, and voriconazole, and began G-CSF support (5 μg/kg) on day 15, given until leukocyte recovery or treatment failure. On the basis of the findings of the UK National Cancer Research Institute (NCRI) AML19 trial, where double induction courses with FLAG-Ida led to prolonged cytopenia and infectious complications,[11] only a single cycle of FLAG-Ida-ven was prescribed with the intention to proceed to alloSCT as soon as possible. When a further therapy was needed as a bridge to alloSCT, a course of cytarabine at a medium intensity (1-1.5 g/m^2 for 6 doses) was given. Data collected included patient demographics, prior therapies and the genetic risk group. Hematologic and non-hematologic toxicities and 30- and 60-day mortality were recorded. For efficacy, CR and CRi rates were assessed, as well as MLFS and CRc rates at bone marrow evaluation post-treatment. All patients were examined for minimal residual disease (MRD) by flow cytometry at a sensitivity threshold of 10^{-3}. Patients were evaluated for overall survival (OS), and those who achieved remission were evaluated separately for progression-free survival (PFS).

The focus of this report is on the 34 patients aged 65-77 years (median 70.5 years) who were treated with the FLAG-Ida-ven regimen. They represent 29% of all similar patients at that age range (N=117) who were treated for acute leukemia during the study period. Fourteen patients were treated for newly diagnosed leukemia, of whom 12 had an adverse-risk karyotype, while 20 were treated for relapsed leukemia, 14 of whom had an adverse-risk karyotype. (See Table 1 for further details.)

A CR was achieved in 10 patients and CRi in 2, while additional 11 patients achieved MLFS post-treatment, with a CRc of 67.6%. Sixty-five percent of the 23 responding patients (N=15) achieved MRD negativity. Twenty of the 23 responding patients were subsequently transplanted. Three patients received one consolidation cycle before alloSCT, and 17 transitioned directly to alloSCT. An additional patient was transplanted while in active disease after FLAG-Ida-ven failure. The median time between day 1 of induction and day 1 of alloSCT conditioning was 52 days. Twelve patients were treated with reduced intensity conditioning, while 7 received non-myeloablative conditioning using the fludarabine / total body irradiation protocol.[12] Only 2 patients received myeloablative conditioning with either FluBus4 or thiotepa-busulfan-fludarabine protocols (Table 2).

The median OS for the total cohort was 147 days, with an estimated 2-years OS of 28%. Median PFS and OS for patients who achieved CRc were 152 days and 255 days, respectively (Figure 1). Notably, 12 of the 20 transplanted patients are still alive and in CR1 (*Online Supplementary Figure S1*).

In univariate analysis, only prior venetoclax exposure was predictive for treatment failure (CRc of 30% *vs*. 83% with prior venetoclax *vs*. no prior treatment with venetoclax; *P*=0.005), while the European LeukemiaNet (ELN) 2022 risk category, *TP53* status and N/D *vs*. R/R AML were not. The median time to both platelet (>50x10^9/L) and neutrophil (>500/μL) recovery was 22 days. Lack of neutrophil recovery was seen in 6 patients, all of whom did not achieve CRc, whereas in 8 out of 16 patients who failed platelet recovery, a CRc was observed. The median length of hospitalization was 26 days.

Non-hematologic toxicities were seen in over 80% of patients. Twenty-two patients experienced bloodstream infections (BSI), and 11 were hemodynamically unstable and required vasopressor support. In 3 patients, the hemodynamic instability was accompanied by respiratory failure, leading to mechanical ventilation. Two patients experienced grade 3-4 mucositis and 2 patients had a decrease in cardiac systolic function. The 30-day and 60-day mortality rates were 8.8% and 14.7%, respectively. All deaths between day 30 and day 60 occurred in non-responders.

Treatment of older patients with AML is challenging and, despite the introduction of LIC-VEN, OS is disappointing, as most of these patients will ultimately succumb to their leukemia;[13] thus, alloSCT remains the only curative option. However, only 10-15% of patients treated with LIC-VEN

Table 2. Transplantation modality.

Variable	N/D cohort N=12	R/R cohort N=9
Gender male/female	10/2	8/1
ELN 2022 risk group, N		
Favorable	1	2
Intermediate	0	2
Adverse	11	5
Type of donor, N		
Matched related	2	1
Matched unrelated	5	6
Haploidentical/mismatched	5	2
Conditioning regimen, N		
Myeloablative	1	1
Reduced intensity	6	6
Non-myeloablative	5	2
GvHD prophylaxis, N		
CNI+MTX	1	1
CNI+MTX+ATG	1	3
CNI+MMF	1	0
CNI+MMF+ATG	5	4
PTCY+CNI+MMF	4	1

CNI+MMF: calcineurin inhibitor + mycophenolate mofetil; CNI+MMF+ATG: calcineurin inhibitor + mycophenolate mofetil + anti-thymocyte globulin; CNI+MTX: calcineurin inhibitor + methotrexate; CNI+MTX+ATG: calcineurin inhibitor + methotrexate + anti-thymocyte globulin; ELN: European LeukemiaNet; GvHD: graft-*versus*-host disease; N: number; N/D: newly diagnosed; R/R: relapsed / refractory; PTCY+CNI+MMF: post-transplant cyclophosphamide + calcineurin inhibitor + mycophenolate mofetil.

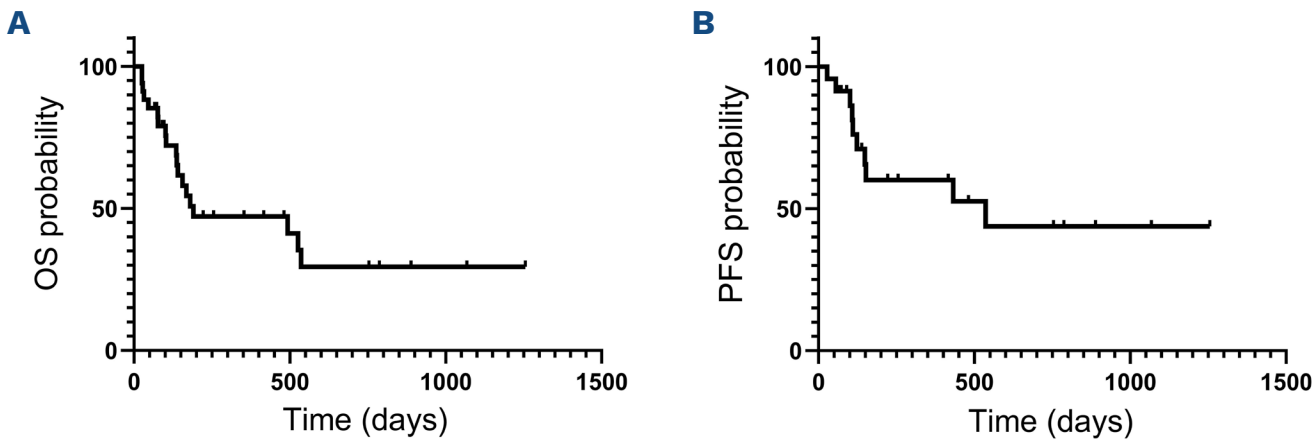

Figure 1. Survival outcomes: results of Kaplan-Meier analysis. (A) Overall survival (OS) of the entire cohort. (B) Progression-free survival (PFS) for patients who achieved composite complete remission (complete remission + CR with incomplete count recovery + morphological leukemia-free state).

will actually undergo alloSCT[2,13] because of advanced age or significant comorbidities. Another common reason for deferring alloSCT is non-remission after LIC-VEN therapy, which occurs in one-third of the patients.[14] However, the use of higher intensity regimens in fit, older patients with acute leukemia is often rejected, as toxicity is higher, which could later preclude the option to proceed to alloSCT. The current study evaluated the efficacy and safety of high-intensity treatment with FLAG-Ida-ven in fit, older patients with AML, with risk factors for treatment failure with LIC+VEN. This study reported a CRc of 67% for the entire cohort, with high rates of MRD negativity, allowing for high transplantation rates (46% of all patients, 87% of patients achieving CRc). Thus, in contrast to theoretic concerns, the intensity of the regimen actually facilitated transplantation in most patients and also promoted a reduction in the intensity of the pre-alloSCT conditioning. Two-thirds of the cohort were conditioned with reduced intensity regimens, while only one patient in CR1 received myeloablative conditioning. This is in contrast to the reported outcome of patients receiving alloSCT after induction with LIC-VEN, 20-30% of whom were conditioned with myeloablative regimens.[13]

High remission rates with FLAG-Ida-ven were obtained in all subgroups, including patients with *TP53*-mutated acute leukemia. The only exception was patients who failed prior treatment with LIC+VEN and were salvaged with FLAG-Ida-ven. This is in line with prior reports on the poor prognosis of LIC-VEN failure.[15]

The hematologic toxicity of the FLAG-Ida-ven regimen was manageable, with a rapid recovery of both neutrophils and platelets at median of 22 days. However, one of the 8 patients who achieved CRc and yet did not recover platelet count until transplantation experienced spontaneous intracranial bleeding after discharge and was successfully treated conservatively. In comparison, the NCRI AML19 trial reported a significantly longer median time to platelet and neutrophil recovery of 29 and 30 days, respectively.[11] Indeed, we set a lower limit for recovery than that of the NRCI trial, as no bleeding or sepsis events were evident beyond that limit.

Infectious complications were observed in the majority of patients, resulting in half of them experiencing hemodynamic instability; this was mostly short-lived. A similar incidence of BSI was reported with other intensive regimens,[2] including FLAG-Ida-ven when given to younger patients.[9] Early mortality rates in this reported cohort were in line with the incidence in other intensively and non-intensively treated cohorts, mostly composed of younger patients.[2,9,11,13]

Study limitations are related to its single-center, single-arm design and the broad variability in idarubicin doses used. However, this reflects real-world practice, where patients differ in their fitness.

This report of 34 consecutive patients in a single center suggests that in fit, older patients with high-risk acute leukemia, intensive chemotherapy with a single cycle of FLAG-Ida-ven can lead to a deep remission and effective, prompt bridging to transplantation, potentially improving survival compared to lower-intensity regimens. These results warrant evaluation in a larger randomized controlled setting.

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Disclosures

No conflicts of interest to disclose.

Contributions

AF is responsible for study concept and design, data acquisition, analysis and interpretation, and supervised the study. NG is responsible for study design, and data acquisition, analysis and interpretation. IH is responsible for data analysis and interpretation, reviewed the manuscript, and provided critical input. BK helped prepare the manuscript. TZ and DY-O reviewed the manuscript and provided critical input.

Data-sharing statement

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

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