Venetoclax with intensive induction chemotherapy in newly diagnosed adult acute myeloid leukemia: early outcomes from a real-world experience

Over the past several decades, there has been a consistent effort to move beyond the conventional "3+7" intensive induction regimen in the treatment of acute myeloid leukemia (AML). The advent of BCL-2 inhibitors has significantly transformed the therapeutic landscape, particularly in combination with hypomethylating agents (HMA), where this regimen has emerged as a standard of care in elderly or unfit patients.[1] Recently, comparative studies have evaluated HMA plus venetoclax (Ven) against intensive induction in younger, fit adults, demonstrating comparable efficacy.[2] Interestingly, preliminary results exploring the integration of anti-leukemic potential of BCL-2 inhibitors with curative efficacy of intensive induction chemotherapy (IC) have shown encouraging activity across all cytogenetic risk groups, with high rates of measurable residual disease (MRD) negativity and a toxicity profile similar to that of IC alone.[3]

This retrospective cohort study from a tertiary care academic institute included all consecutive newly diagnosed adult patients (≥18 years) with AML deemed fit for intensive induction chemotherapy and treated between November 9, 2022 and June 15, 2025. Baseline clinical characteristics, treatment details, and outcomes were extracted from medical records and reviewed. Diagnosis and risk stratification were performed according to the European LeukemiaNet (ELN) 2022 criteria.[4] The study was approved by the institutional ethics committee.

Induction chemotherapy consisted of daunorubicin 60 mg/m² intravenously (IV) for 3 days and cytarabine 100 mg/m² as a continuous IV infusion for 7 days. The administration schedule of Ven was 100 mg once daily from day 1 to day 14. Dose escalation of Ven was facilitated by concurrent administration of oral voriconazole 200 mg twice daily from day 4. Patients who failed to achieve complete remission (CR) and/or were MRD-positive on day 28 received a second cycle of induction. Response assessment was performed via bone marrow examination either upon recovery of platelet and absolute neutrophil counts (ANC) or on day 28, whichever occurred first. MRD evaluation was conducted by multiparametric flow cytometry.

For consolidation, patients in the adverse-risk (AR) and intermediate-risk (IR) categories received 3-4 cycles of high-dose cytarabine (HiDAC) at 9 g/m² per cycle, while favorable-risk (FR) patients received 12 g/m² per cycle.

Early mortality was defined as death occurring within 28 days of start of induction. CR was defined according to the ELN 2022 criteria. CR with incomplete hematologic recovery (CRi) was defined as meeting all criteria for CR except for persistent neutropenia (absolute neutrophil count <1.0×10^9/L) and/or thrombocytopenia (platelet count <100×10^9/L) on or after day 28. Composite complete remission (cCR) was defined as the sum of CR and CRi. Overall CR was defined as patients achieving a CR/CRi after reinduction with a regimen of physician's choice. MRD positivity was defined as ≥0.1% of CD45 expressing cells with the target immunophenotype according to the ELN 2022 criteria.

Eighty consecutive fit adult patients with newly diagnosed AML were included. Baseline characteristics are summarized in the *Online Supplementary Table S1*. The median white blood cell (WBC) count was 28.48×10^9/L (range, 0.83-339.7×10^9/L). According to ELN 2022 risk stratification, 33.8% of patients were classified as FR, 50% as IR, and 16.3% as AR. Patients with CBF-AML accounted for 21.2% (17/80), while *NPM1* mutations were observed in 11.2% (9/80) of patients. Additionally, *bZIP CEBPA* mutations were identified in 11.2% (9/80) of the cohort. Molecular analysis failed in four patients. Detailed molecular profiles are shown in the *Online Supplementary Table S1* and *Online Supplementary Figure S2*.

Early mortality occurred in 12 patients, and disease response could not be evaluated in these individuals. All deaths were attributed to fulminant sepsis, with 25% of cases showing culture positivity for multidrug-resistant organisms; all patients had febrile neutropenia. The composite CR rate (CR + CRi) was 70% (56/80), with an overall CR rate of 75% (60/80). Stratification by risk groups showed CR rates of 88.9%, 67.5%, and 38.5% for FR, IR, and AR groups, respectively (Table 1). The median time to platelet recovery (defined as platelets ≥100×10^9/L) was 26 days (range, 16-78 days), and the median time to ANC recovery (defined as ANC ≥1×10^9/L) was 25 days (range, 15-93 days). The median length of hospital stay during induction was 30 days (range, 7-60 days). Five patients received less than 14 days of Ven owing to early mortality. The median duration of drug intake was 14 days (range, 3-14 days). Among the 56 patients achieving CR, the MRD-negative rate was 92.8% (52/56).

Of the four patients in CR who were MRD-positive, two received reinduction therapy (1 with FLAG-Ven, the other with 7+3+Ven) and subsequently converted to MRD-negative status. Among the 12 patients who did not achieve CR after the first cycle, eight received a second induction regimen, including FLAG-Ida (3 patients), 7+3+Midostaurin (1 patient), 7+3+Ven (2 patients), and azacitidine-Ven plus Sorafenib (1 patient). Four of these patients achieved CR after reinduction. At the time of data cut-off, none of the

patients in CR were transplanted.

At a median follow-up of 11 months (range, 0.1–31.6), the median overall survival (OS) was 21.3 months (95% confidence interval [CI]: 12.2-not reached [NR]). OS differed significantly across risk groups (Table 2). The median event-free survival (EFS) was 10.9 months (range, 7.7-14.4), with significant differences between all risk groups (Figure 1).

At the data cut-off of June 15, 2025, 16 (26.7%) of the 60 patients who achieved CR relapsed. The median relapse-free survival (RFS) was NR in the FR group (range, 13.2 months-NR), 12.7 months (range, 9.7-NR) in the IR group, and 8.5 months (range 7.8-NR) in the AR group. The overall cohort's median RFS was NR (range, 10.1 months-NR).

Among the 24 patients with *FLT3*-internal tandem duplication mutations, 16 (66.7%) achieved CR following the first induction cycle and four had early induction mortality. Due to financial constraints, none among these patients received FLT3 inhibitors. Four patients who did not achieve CR initially received reinduction therapy, with two achieving remissions. The median OS and EFS for this cohort were 14.2 months and 9.5 months, respectively (*Online Supplementary Figure S1*). Our findings in this study demonstrate robust and deeper responses across all risk groups.

Historically, CR rates with standard intensive induction therapy have ranged from 60% to 70%. Our results compare favorably with both regional and international studies.[5,6]

Ven demonstrated impressive activity across all risk categories, with particularly remarkable efficacy in the FR subset. All evaluable patients in this group not only achieved CR after a single induction cycle but also achieved measurable MRD negativity.

Recent evidence has established MRD as a powerful surrogate for long-term outcomes in AML. Moreover, achieving MRD negativity prior to allogeneic transplant is increasingly recognized as a key predictor of durable remission and survival.[7] Consistent with prior studies, our cohort showed a high rate of MRD negativity, which is encouraging.[5,8] In contrast, conventional chemotherapy has been associated with significantly lower rates of MRD clearance.[9]

Our study also provides insights into the efficacy of Ven combined with cytotoxic chemotherapy in patients with *FLT3*-mutated AML - a subset commonly encountered in clinical practice. Historically, CR rates in this group with standard intensive induction have ranged from 55% to 60%.[10] Early trials of Ven with HMA showed suboptimal responses in *FLT3*-mutated AML.[11] However, our findings suggest that combining Ven with intensive chemotherapy may overcome inherent resistance mechanisms in this subgroup. This is in line with a recently published study that also reported high response rates with this regimen.[12]

The optimal dose and schedule of Ven in combination with intensive chemotherapy remain subjects of ongoing investigation. In our study, we did not observe a significant incidence of tumor lysis syndrome despite starting Ven from day 1. An ongoing clinical trial is currently comparing the efficacy of 8-day *versus* 14-day Ven schedules which may help establish the optimal duration and dosing strategy.[13]

We did not include Ven during consolidation primarily due to concerns regarding delayed hematologic recovery when Ven is combined with high-dose cytarabine, as noted in the

Table 1. Treatment and survival outcomes.

	Overall N=80	FR* N=27	IR* N=40	AR* N=13	*P*
Treatment outcomes					
CR after 1st Induction, N (%)					
CR	41 (51.2)	18 (66.7)	19 (47.5)	4 (30.8)	0.026
CRi	15 (18.7)	6 (22.2)	8 (20)	1 (7.7)	-
cCR (CR+CRi)	56 (70.0)	24 (88.9)	27 (67.5)	5 (38.5)	-
Survival outcomes, N=80					
Median OS, months (95% CI)	21.3 (12.2-NR)	25.3 (15.4-NR)	15.1 (8.8-NR)	5.1 (1.4-NR)	0.043 (log-rank)
1-year OS, % (IQR)	62.8 (50.6-72.2)	74.5 (51.8-87.6)	65.3 (47.9-78.2)	30.4 (8.4-56.5)	-
2-year OS, % (IQR)	46.8 (33.3-59.2)	66.6 (40.7-83.2)	42.3 (24.5-59.0)	30.4 (8.4-56.5)	-
Median EFS, months (95% CI)	10.9 (7.7-14.4)	NR (9.1-NR)	9.8 (3.6-14.0)	1.0 (0.7-9.5)	<0.001 (log-rank)
1-year EFS, % (IQR)	46.6 (34.9-57.5)	70.2 (47.5-84.5)	41.3 (25.7-56.3)	16.7 (2.7-41.3)	-
2-year EFS, % (IQR)	36.5 (24.3-48.8)	61.4 (35.2-79.7)	28.9 (14.3-45.3)	16.7 (2.7-41.3)	-

*Prognostic stratification according to European LeukemiaNet 2022 risk category. FR: favorable risk; IR: intermediate risk; AR: adverse risk; CR: complete remission; CRi: CR with incomplete hematologic recovery; cCR: composite CR; OS: overall survival; CI: confidence interval; IQR: interquartile range; NR: not reached; EFS: event-free survival.

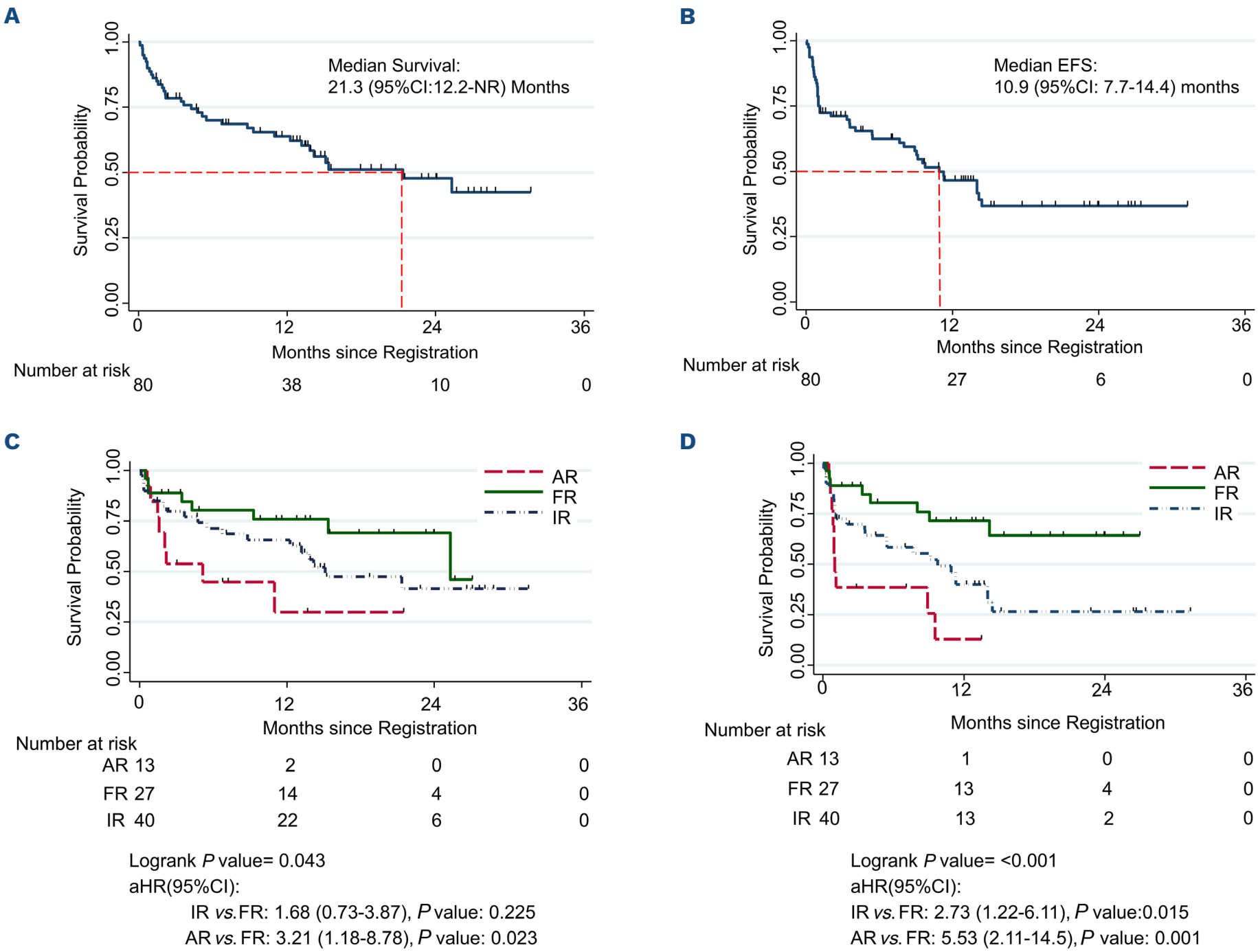

Figure 1. Kaplan Meier curves depicting overall survival and event-free survival. (A) Overall survival (OS) in the entire cohort of 80 patients. (B) Event-free survival (EFS) of the entire cohort of 80 patients. (C) OS by European LeukemiaNet (ELN) 2022 risk stratification. (D) EFS by ELN 2022 risk stratification. FR: favorable risk; IR: intermediate risk; AR: adverse risk; aHR: adjusted hazard ratio NR: not reached.

CAVEAT trial.[14]

All induction-related deaths, and a few during consolidation, in our cohort were attributed to uncontrolled sepsis. This finding is consistent with other studies from the region and underscores the high burden of multidrug-resistant organisms and the healthcare delivery challenges faced in low- and middle-income countries (LMIC).[6,15]

Our study has limitations, including its retrospective design, short follow-up duration, and lack of access to targeted agents and bone marrow transplant for most patients. Furthermore, some patients who died during induction could not be evaluated for disease response, which could have impacted the results.

In conclusion, Ven combined with intensive chemotherapy appears to be a promising therapeutic option for fit adult patients with AML. The high rate of CR and MRD negativity observed in this study supports its further evaluation in larger, prospective, randomized trials. The results of this study may help refine the treatment strategies for AML, especially in patients with high-risk disease or those with *FLT3* mutations.

Authors

Aakanksha Naik,[1] Babita Kataria,[2] Vinod Sharma,[2,3] Aparna Sharma,[2] Atul Batra,[1] Kanupriya Bhatia,[1] Bhoor Singh,[1] Anita Chopra,[4] Diptiranjan Rout,[5] Hari Sagiraju,[6] Rounik Talukdar,[6] Sarjana Tiwari[7] and Akash Kumar[2]

[1]Department of Medical Oncology, IRCH, All India Institute of Medical Sciences, New Delhi; [2]Department of Medical Oncology, National Cancer Institute, AIIMS - Jhajjar Campus, All India Institute of Medical Sciences, District - Jhajjar, Haryana; [3]HCG Cancer Institute,

Jaipur, Rajasthan; [4]Department of Laboratory Oncology, IRCH, All India Institute of Medical Sciences, New Delhi; [5]Department of Transfusion Medicine, National Cancer Institute, AIIMS - Jhajjar Campus, All India Institute of Medical Sciences, District - Jhajjar, Haryana; [6]Department of Preventive Oncology, National Cancer Institute, AIIMS - Jhajjar Campus, All India Institute of Medical Sciences, District - Jhajjar, Haryana and [7]Department of Hematopathology, MAX Super-specialty hospital, Patparganj, New Delhi, India

Correspondence:
A. KUMAR - akashjha08@yahoo.com

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Disclosures

No conflicts of interest to disclose.

Contributions

AN and AK conceived the study and contributed to the design and interpretation of the data, the literature review and the preparation of the manuscript draft. HS and RT contributed to data collection and analysis. BK, VS, AS, AB, KB, BS, AC, DR and ST participated in patient management, literature review and clinical assessments. All authors reviewed and approved the final version of the manuscript.

Data-sharing statement

Data set will be available from corresponding author on reasonable request.

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