Sequential therapy with allogeneic HCT in patients aged ≥70 years with active AML: a single-center retrospective analysis

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Abstract

Patients ≥70 years with relapsed/refractory acute myeloid leukemia (AML) have an extremely poor prognosis. We adopted a sequential therapy approach, aiming to proceed directly to allogeneic hematopoietic cell transplantation (HCT) despite active disease. We analyzed results of all consecutive patients aged over 70 years and diagnosed with primary refractory/relapsed AML who underwent HCT with sequential therapy approach (FITCy regimen) in the Tel Aviv Sourasky Medical Center. Fifty-one patients (median age 72 years; primary refractory N=42; relapse N=9). Median follow-up was 35 (range, 12-91) months. Incidences of overall and grade 3-4 acute graft-*versus*-host disease (GVHD) were 39.2% (95% confidence interval [CI]: 25.6-52.8), and 5.9% (95% CI: 0.0-12.5), respectively. Incidences of overall and moderate-severe chronic GVHD were 40.0% (95% CI: 25.7-57.1) and 29.4% (95% CI: 13.2-46.9), respectively. Non-relapse mortality at 3 years was 36% (95% CI: 22-49). Forty-two of 51 patients (82.4%) had CR on day +30 post HCT. Relapse incidence at 3 years was 27.8% (95% CI: 14.3-41.2). GVHD-free relapse-free and overall survival (OS) at 3-years were 30% (95% CI: 19-47) and 31% (95% CI: 17-55), respectively. Multivariable analysis showed that worse European LeukemiaNet 2022 score, relapsed AML (*vs.* primary-refractory), not receiving ATG, and lower albumin prior to conditioning, were associated with higher mortality. We developed a model to predict OS that showed median OS in the low-, intermediate-, and high-risk group, not reached, 32.9 months, and 2.1 months, respectively, *P*<0.001. We conclude that sequential therapy in elderly patients with active AML demonstrates a strong anti-leukemic effect, and age alone should not be a barrier to this strategy.

Introduction

Primary refractory acute myeloid leukemia (AML) occurs in ~30% of patients and carries a poor prognosis.[1,2] Salvage chemotherapy, including novel agents, achieves limited responses, with median overall survival (OS) of about 12.5 months.[2,3] Allogeneic hematopoietic cell transplantation (HCT) is the only treatment consistently associated with improved survival,[4,5] but outcomes are poor without pre-transplant remission, and many patients never reach HCT eligibility.[4,6,7]

In elderly patients, particularly those ≥70 years with refractory AML, prognosis is dismal: median OS with standard care may be only 2 months, and long-term survival is rare.[8-10] Frailty, comorbidities, and treatment-related toxicity often preclude intensive salvage regimens, and active disease at transplant predicts inferior outcomes.

To address these challenges, several sequential approaches have been developed worldwide, the first being FLAMSA,[11,12] which combines cytoreductive chemotherapy with reduced-intensity conditioning to allow rapid progression to HCT. Our center adapted this concept into the FITCy regimen (fludarabine, cytarabine ± idarubicin, cyclophosphamide, and 4 Gy total body irradiation) for elderly patients with available donors. In a previous German-Israeli multicenter study, we reported encouraging outcomes with a FLAMSA-based sequential strategy in primary induction failure.[13]

Here, we present our single-center experience using a FITCy sequential conditioning regimen in patients ≥70

years with primary refractory or relapse AML, focusing on feasibility, disease control, and post-transplant outcomes.

Methods

Patients

Patients aged 70 years or older with either primary refractory or relapsed AML were included in this study. Patients were given FITCy conditioning regimen before HCT. Primary refractory AML was defined as unresponsiveness (at least 10% of blasts in marrow) after at least one course of 7+3 (defined on day 28-35 marrow) or two courses of venetoclax-azacitidine (Ven-azacitidine) regimen. Patients with relapsed AML either proceeded directly to HCT or, if a donor had not yet been identified, received salvage chemotherapy. Percentage of blasts was documented just before starting of conditioning. No patients were *a priori* excluded based on comorbidities; all were evaluated for eligibility under this approach. Nevertheless, 25% of the patients were referred from other centers and were subjected to physician decision to consider sequential therapy approach. All patients gave informed consent to the planned treatment schedule as well as for reporting of transplantation outcomes and the study was approved by the local ethic committee.

Details regarding the donor search, the comprehensive treatment, supportive care, and evaluation of disease and response can be found in the *Online Supplementary Appendix*.

Statistics

Continuous variables were described as the mean, median, standard deviation and range of number observations, as applicable. Categorical data were described with contingency tables including frequency and percent. Confidence intervals (CI) were calculated at the (two-sided) 95% level of confidence. A two-sided *P* value of <0.05 was considered to be statistically significant. OS was defined as the time from HCT until the date of subject death from any cause. For subjects who have not died, survival data were censored at the subject's last known date of follow-up. Disease response and disease progression were assessed according to the previously published response criteria. The probabilities of GRFS and OS were estimated using the Kaplan-Meier method, and the log-rank test was used to evaluate the differences between groups. Probabilities of graft-*versus*-host disease (GVHD) were estimated with the use of cumulative incidence curves, with relapse and death treated as competing risks. Probabilities of non-relapse mortality (NRM) were estimated with the use of cumulative incidence curves, with relapse treated as a competing risk. Relapse incidence was evaluated with use of cumulative incidence curves, with death treated as a competing risk. The Fine and Gray's method was used to evaluate the differences between groups. Uni- and multivariable analyses were performed using a Cox proportional hazard regression model for OS, and competing risk regression by the method of Fine and Gray for GVHD, NRM, and relapse. We used SPSS version 29 and R software (version 4.5.1; R Foundation for Statistical Computing, Vienna, Austria) to perform the analyses.

For the comparison of patients with primary refractory AML who received sequential therapy (HCT cohort) with non-HCT series of the three previously published papers,[14-16] restricted mean survival time (RMST) at 24 months was computed.[17] To adjust for baseline differences, a matching-adjusted indirect comparison (MAIC) using iterative proportional fitting (raking) aligned the HCT cohort distribution of sex and European LeukemiaNet (ELN) 2022 risk with that of the Park *et al*. (venetoclax arm).[15] For the decitabine cohorts,[14,16] where co-variate data were incomplete, exponential survival functions anchored to published medians were used for benchmarking. Hazard rates ($\lambda = \ln 2/\text{median OS}$) were applied to derive approximate hazard ratios (HCT cohort/control). All comparator cohorts encompassed both refractory and relapsed AML; hence, the analysis likely underestimates the relative survival advantage associated with transplantation in strictly primary-refractory disease.

Results

Between May 2015 and December 2024 there were 51 patients (primary refractory N=42; relapsed AML N=9) who fulfilled eligibility criteria to this analysis. Table 1 depicts the patients' characteristics. Median follow-up of surviving patients was 35 (range, 12-91) months. Median age was 72 (range, 70-77) years. Median days from AML diagnosis to HCT in patients with primary refractory or relapsed disease was 86 (range, 30-188) days, and 209 (range, 125-1,960) days, respectively. The majority of patients received venetoclax and ATG (63% and 88%, respectively) as part of the preparative regimen and majority (71%) received allograft from a matched unrelated donor. In all cases the graft was derived from peripheral blood stem cells (PBSC).

Early transplant course and clinical events

Seventeen patients (33%) developed microbiologically documented infections (MDI), including eight with gram-negative rods (GNR) and ten with gram-positive cocci (GPC); one patient had a mixed infection. Among the GNR cases, two involved extended-spectrum β-lactamase (ESBL)-producing organisms and one involved a carbapenemase-producing *Enterobacterales* (CPE). None of the GPC isolates exhibited antibiotic resistance. Two patients (4%) developed invasive fungal infections - one probable *Aspergillus* infection and one *Candida fermentati* infection. Two cases of GNR bacteremia were fatal. Among the 17 patients with MDI, only one patient (6%) had a preconditioning-absolute neutrophil count above 0.5×10^9/L. Seven patients (14%) developed

mucositis (grade 1 N=2; grade 2 N=5). None developed grade 3-4. Five patients (10%) developed SOS (mild N=1; moderate N=3; severe N=1).

Median time to neutrophil engraftment was 11 (range, 8-21) days and median time to platelet engraftment was 18 (range, 11-46) days. Two patients with early progression of AML (within the first 2 weeks) were not evaluated for engraftment. Two additional patients had neutrophil engraftment but never attained sustained platelet engraftment; both subsequently relapsed at 2.7 and 3.2 months post-HCT. None of the 49 patients had primary or secondary graft failure. Whole marrow chimerism at day 30 post HCT showed median of 100% (range, 56-100%) of donor-derived cells. Among the six patients who had donor chimerism levels below 90% on day +30 post-HCT without evidence of disease, three (50%) subsequently relapsed at 2.7, 3.2, and 32.2 months after HCT.

Graft-*versus*-host disease

Median onset of grade 2-4 acute GVHD was 41 (range, 7-140)

Table 1. Characteristics of patients.

Domain	All patients N=51	Primary refractory N=42	Relapsed N=9
Sex: male, N (%)	32 (63)	27 (64)	5 (56)
Age, years, median (range)	72 (70-77)	72 (70 -77)	73 (70-74)
Median days from AML diagnosis to HCT (range)	125 (30-1,960)	86 (30-188)	209 (125-1,960)
ELN 2022 risk, N (%) Favorable Intermediate High	 5 (10) 19 (37) 27 (53)	 3 (7) 19 (45) 20 (48)	 2 (22) 0 (0) 7 (78)
Prior therapy, N (%) Prior refractory to - 7+3-based induction Prior refractory to - Azacitidine+Ven	 N/A N/A	 23 (55) 19 (45)	 N/A N/A
N of lines prior, median (range)	N/A	N/A	2 (1-3)
% blasts in marrow prior to HCT, median (range)	30 (13-92)	34 (13-92)	24 (15-81)
Preparative regimen - Ven included, N (%)	32 (63)	25 (60)	7 (78)
Preparative regimen - ATG included, N (%)	45 (88)	37 (88)	8 (89)
Hb, gr/dL, median (range)	8.2 (6.7-11.9)	8.2 (6.7-11.9)	8.3 (7.3-10.1)
ANC x10^9/L, median (range)	0.2 (0-1.4)	0.2 (0-1.2)	0.3 (0-1.4)
WBC x10^9/L, median (range)	1.7 (0-20.3)	1.8 (0-14.6)	1.6 (0.1-20.3)
Albumin, g/L, median (range)	36.4 (24-48)	35.7 (24-48)	36.6 (32.7-41)
LDH U/L, median (range)	354 (107-2,968)	351 (107-2,968)	394 (238-893)
CRP mg/L, median (range)	16 (0.3-295)	13 (0.3-245)	26 (1.4-295)
Karnofsky score, median (range)	80 (50-100)	80 (50-100)	90 (80-100)
HCT-CI, median (range)	3 (0-7)	3 (0-7)	4 (0-6)
High modified AL-EBMT score, N (%)	13 (25)	13 (31)	0 (0)
Donor's characteristics, N (%) Matched-related Matched-unrelated Haploidentical Female-to-Male	 8 (16) 36 (71) 7 (14) 2 (4)	 7 (17) 30 (71) 5 (12) 2 (5)	 1 (11) 6 (67) 2 (22) 0 (0)
CMV status, N (%) D+/R+ D+/R- D-/R+ D-/R-	 41 (80) 1 (2) 7 (14) 2 (4)	 34 (81) 1 (2) 6 (14) 1 (2)	 7 (78) 0 (0) 1 (11) 1 (11)

AL-EBMT: acute leukemia-European Bone Marrow Transplantation risk score; AML: acute myeloid leukemia; ANC: absolute neutrophil count; ATG: anti-thymocyte globulin; CMV: Cytomegalovirus; CRP: C-reactive protein; D: donor; ELN: European LeukemiaNet; HCT: hematopoietic cell transplantation; HCT-CI: HCT-comorbidity index; Hb: hemoglobin; LDH: lactate dehydrogenase; R: recipient; N/A: not applicable; U/L: units per liter; WBC: white blood cells; Ven: venetoclax.

days. Three cases were identified as late acute GVHD, emerging after cyclosporine tapering had begun. Among the 20 patients who developed acute GVHD, involvement of skin, gut, and liver occurred in 14 (70%), nine (45%), and none (0%) of the patients, respectively. By day 200, the cumulative incidences of overall and grade 3-4 acute GVHD were 39.2% (95% CI: 25.6-52.8), and 5.9% (95% CI: 0.0-12.5), respectively (Figure 1A). In univariable analyses, none of the candidate predictors were significantly associated with overall acute GVHD (Table 2). The low number of events precluded multivariable analysis.

Median time for the development of chronic GVHD was 6.7 (range, 4.1-11.7) months. At 12 and 36 months after HCT, the cumulative incidences of overall and moderate-severe chronic GVHD were 40.0% (95% CI: 25.7-57.1) and 25.8% (95% CI: 11.0-42.1), and 40.0% (95% CI: 25.7-57.1) and 29.4% (95% CI: 13.2-46.9), respectively (Figure 1B). In univariable analysis, administration of ATG was associated with a lower incidence of overall chronic GVHD (HR=0.43; 95% CI: 0.3-0.8; *P*=0.004), whereas age, donor type, female-to-male transplantation, and patient sex were not predictive. The low number of events precluded multivariable analysis.

Non-relapse mortality

Eighteen patients died because of NRM (prior GVHD N=8; sepsis with no prior GVHD, N=8; head injury N=1; undetermined cause N=1). Six deaths occurred within 30 days post HCT - all sepsis-related with no evidence of GVHD; two with prior moderate SOS.

The cumulative incidences of NRM at 1, 3 months, 1 year, and 3 years were 11.8% (95% CI: 2.8-20.7), 26% (95% CI: 13.4-37.6), 33% (95% CI: 20-47), and 36% (95% CI: 22-49) (Figure 1C). Higher albumin prior to HCT was associated with lower NRM (HR=0.86; 95% CI: 0.80-0.97; *P*=0.017) and increased days to HCT was associated with higher NRM (HR=1.1; 95% CI: 1.03-1.4; *P*=0.04, while age, sex, HCT-CI, white blood cell count (WBC) prior to HCT, and primary *versus* relapsed AML were not predictive. The low number of events precluded multivariable analysis.

Disease response and relapse incidence

At day +30 after HCT, in an intent-to-treat analysis, 42 of

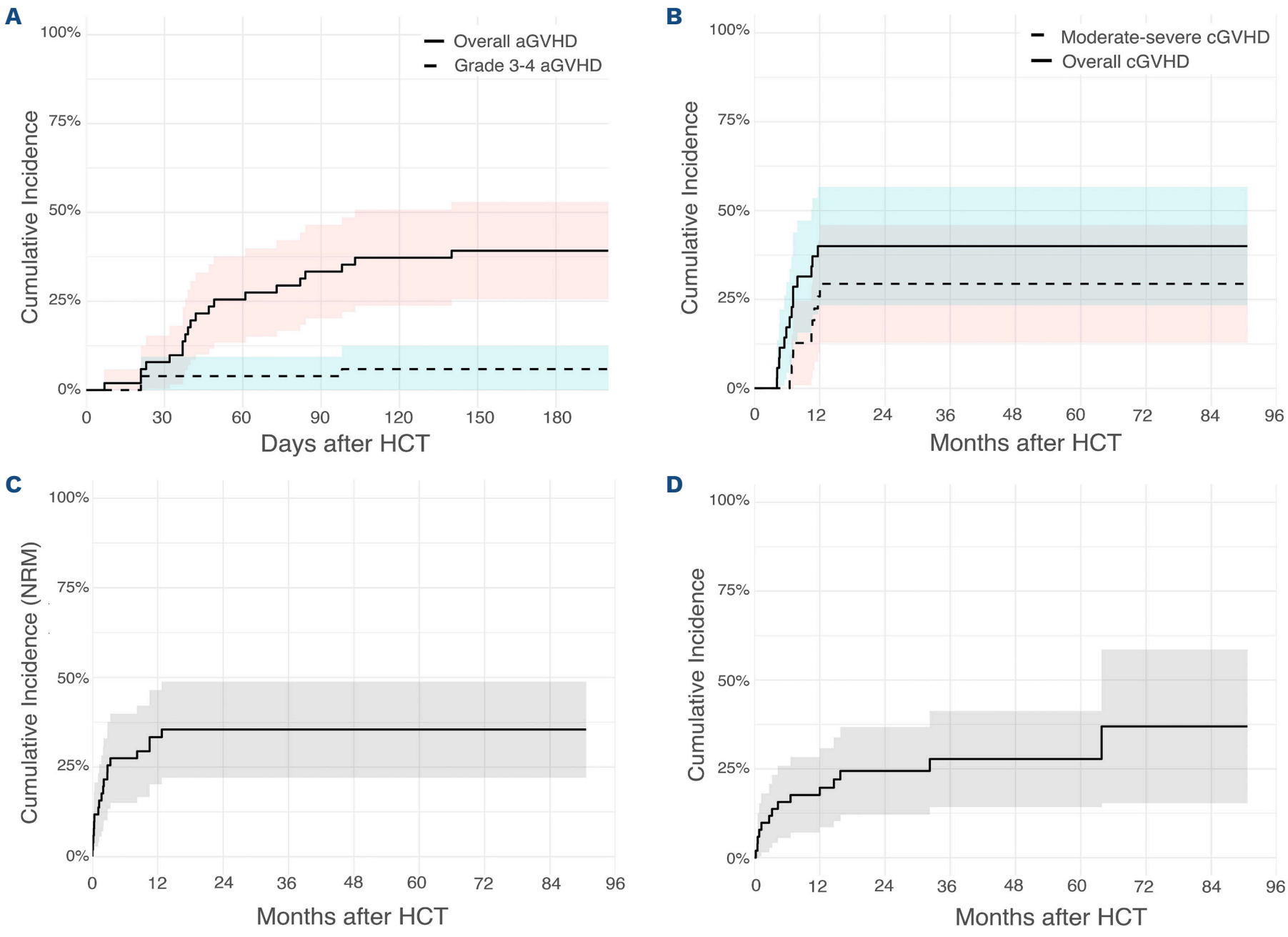

Figure 1. Toxicity and relapse after treatment. (A) Overall and grade 3-4 acute graft-*versus*-host disease (aGVHD). (B) Overall and moderate-severe chronic GVHD (cGVHD). (C) Non-relapse mortality (NRM). (D) Relapse. HCT: hematopoietic stem cell transplantation.

Table 2. Univariable and multivariable analyses.

Domain	Parameter	Univariable analysis			Multivariable analysis		
		HR	95% CI	*P*	HR	95% CI	*P*
Acute GVHD	Age	1.02	0.8-1.4	0.89	-	-	-
	Sex: female *vs.* male	0.46	0.2-1.2	0.11	-	-	-
	ATG	0.55	0.1-2.2	0.4	-	-	-
	Donor: non- *vs.* matched sibling	1.22	0.4-3.9	0.83	-	-	-
	First line treatment	0.67	0.3-1.6	0.36	-	-	-
	Female-to-male	1.6	0.2-2.7	0.68	-	-	-
	Relapsed *vs.* primary refractory	0.83	0.2-2.9	0.77	-	-	-
Chronic GVHD	Age	0.85	0.7-1.1	0.23	-	-	-
	Sex: female *vs.* male	0.96	0.3-2.7	0.94	-	-	-
	ATG	0.43	0.3-0.8	0.004	-	-	-
	Donor: non- *vs.* matched sibling	0.62	0.2-2.3	0.47	-	-	-
	Female-to-male	1.86	0.2-2.8	0.63	-	-	-
Non-relapse mortality	Age	1.04	0.8-1.4	0.79	-	-	-
	Sex: female *vs.* male	0.75	0.3-1.9	0.55	-	-	-
	Relapsed *vs.* primary refractory	1.6	0.5-4.9	0.43	-	-	-
	Days-to-HCT	1.1	1-1.4	0.04	-	-	-
	Albumin prior to conditioning	0.86	0.8-0.97	0.017	-	-	-
	WBC prior to conditioning	0.98	0.8-1.1	0.80	-	-	-
	ANC prior to conditioning	1.03	0.94-1.15	0.41	-	-	-
	HCT-CI	0.95	0.8-1.2	0.68	-	-	-
Relapse	Age	0.97	0.7-1.3	0.84	-	-	-
	First line treatment: Ven-based *vs.* 7+3	1.04	0.4-2.9	0.94	-	-	-
	Relapsed *vs.* primary refractory	2.5	1.3-7.9	0.03	-	-	-
	Days-to-HCT	1	0.98-1.1	0.66	-	-	-
	% blasts prior to conditioning	1.2	0.1-5.7	0.35	-	-	-
	D+30 donor chimerism: <90% *vs.* higher	1.1	1.05-1.3	0.04	-	-	-
GRFS	Age	0.95	0.7-1.2	0.62	-	-	-
	Sex: female *vs.* male	2.7	1.4-5.3	0.005	1.3	0.8-1.7	0.13
	Higher ELN 2022 score	2.1	1.2-3.8	0.009	2.02	1.1-3.7	0.02
	Relapsed *vs.* primary refractory	3.3	1.4-7.4	0.005	3.7	1.6-9.1	0.003
	First line treatment: Ven-based *vs.* 7+3	0.46	0.2-0.9	0.03	-	-	-
	Days-to-HCT	1.0	1.0-1.0	0.13	-	-	-
	Donor: non- *vs.* matched sibling	1.1	0.4-2.6	0.87	-	-	-
	Albumin prior to conditioning	0.9	0.8-0.98	0.01	0.93	0.9-1.02	0.14
	ATG	0.24	0.1-0.6	0.002	0.32	0.1-0.9	0.03
	Ven added to condtioning	0.71	0.4-1.4	0.32	-	-	-
	HCT-CI	1.02	0.9-1.2	0.79	-	-	-
	AL EBMT score	1.3	0.6-2.9	0.46	-	-	-
Overall survival	Age	0.95	0.8-1.2	0.62	-	-	-
	Sex: female *vs.* male	2.7	1.4-5.3	0.005	1.4	0.8-1.9	0.15
	Higher ELN 2022 score	2.1	1.2-3.8	0.009	2.58	1.2-5.6	0.02
	Relapsed *vs.* primary refractory	3.3	1.4-7.4	0.005	2.65	1.1-6.6	0.04
	First line treatment: Ven-based *vs.* 7+3	0.46	0.2-0.9	0.03	-	-	-
	Days-to-HCT	1.03	0.99-1.1	0.12	-	-	-
	Donor: non- *vs.* matched sibling	1.1	0.5-2.6	0.87	-	-	-
	Albumin prior to conditioning	0.9	0.8-0.98	0.01	0.9	0.8-0.99	0.04
	ATG	0.24	0.1-0.6	0.002	0.32	0.1-0.9	0.03
	ANC prior to conditioning	0.84	0.4-1.2	0.25	-	-	-
	Ven added to conditioning	0.71	0.4-1.4	0.32	-	-	-
	HCT-CI	1.02	0.9-1.2	0.79	-	-	-
	AL EBMT score	1.3	0.6-2.9	0.46	-	-	-

AL-EBMT: acute leukemia-European Bone Marrow Transplantation risk score; ANC: absolute neutrophil count; ATG: anti-thymocyte globulin; CI: confidence interval; D+30: day +30 post-transplant; ELN: European LeukemiaNet; GRFS: GVHD-free/relapse-free survival; GVHD: graft-*versus*-host disease; HCT: hematopoietic cell transplantation; HCT-CI: HCT-comorbidity index; HR: hazard ratio; OS: overall survival; Ven: venetoclax; WBC: white blood cells.

51 patients (82.4%; 95% CI: 69.7-90.4) demonstrated complete response (CR). Seven patients (NRM N=6 and relapse N=1) died before day +30, and two additional patients experienced relapse by that time. Among the 44 patients who were alive at day +30, 42 (95.5%; 95% CI: 84.9-98.7) demonstrated CR.

There were 14 cases of relapse. Relapse incidence at 3 months, 6 months 1 year, and 3 years post HCT were 11.8% (95% CI: 2.8-20.7), 15.7% (95% CI: 5.6-25.8), 19.7% (95% CI: 8.6-30.8), and 27.8% (95% CI: 14.3-41.2), respectively (Figure 1D). There were two cases of late relapses, that occurred 32 and 64 months post HCT. Among the relapsing patients, seven patients (50%) had AML with myelodysplatic syndrme-related gene mutations. Lower chimerism test on day +30 and relapsed AML (as opposed to primary refractory) were both associated with increased relapse risk (HR=1.1; 95% CI: 1.05-1.28; *P*=0.04, and HR=2.5; 95% CI: 1. 3-7.9; *P*=0.03, respectively), while ATG, age, percentage of blasts prior to HCT, first line treatment prior to HCT, and days to HCT, did not impact risk of relapse. The low number of events precluded multivariable analysis.

Intervention at the time of relapse was chemotherapy (N=5), chemotherapy with DLI (N=4). One patient received chemotherapy with stem cell boost and one patient proceeded to a second allogeneic HCT. Median time from relapse to death was 2.98 (range, 0.1-85.2) months. Median time from relapse to death in patients given cellular therapy was 5.9 (range, 0.6-33.3) months.

Survival analysis

At the time of data analyses, 21 (41%) patients were alive. GRFS at 6, 12 and 36 months post HCT were 58% (95% CI: 46-73), 38% (95% CI: 27-54), and 30% (95% CI: 19-47) (Figure 2A). Patients with primary refractory disease had better GRFS at 6 and 12 months post HCT compared to patients with relapsed AML (66%; 95% CI: 53-82 *vs*. 22%; 95% CI: 7-75 and 44%; 95% CI: 31-62 *vs*. 11%; 95% CI: 2-71; *P*=0.003) (Figure 2B). Multi-variable analysis identified adverse ELN 2022 score, relapsed disease (*vs*. primary refractory) associated with worse GRFS (HR=2.02; 95% CI: 1.1-3.7; *P*=0.02, and HR=3.7; 95% CI: 1.6-9.1; *P*=0.003, respectively) and ATG as associated with better GRFS (HR=0.32; 95% CI: 0.1-0.9; *P*=0.03) (Table 2).

Incidences of OS at 3 months, 1 year, 3, and 5 years post HCT were 69% (95% CI: 57-83), 53% (95% CI: 41-69), 42% (95% CI: 30-60), and 31% (95% CI: 17-55), respectively (Figure 2C). Subgroup analysis showed that patients with primary refractory disease had better 3- and 12-months OS com-

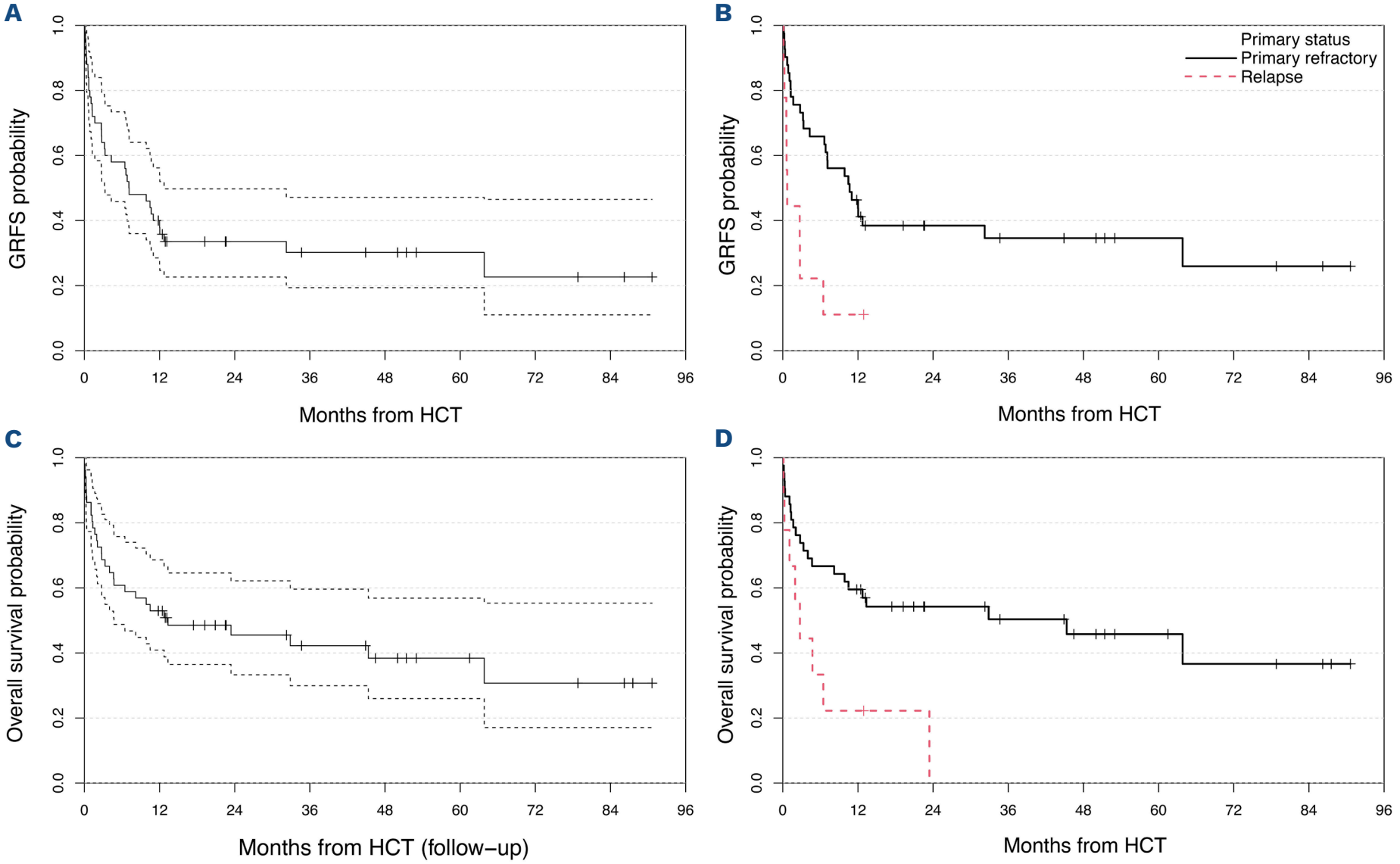

Figure 2. Survival analyses after treatment. (A) Graft-*versus*-host and relapse-free survival (GRFS). (B) GRFS in patients with primary refractory *versus* relapse acute myeloid leukemia. (C) Overall survival. (D) Overall survival in patients with primary refractory *versus* relapse acute myeloid leukemia. HCT: hematopoietic stem cell transplantation.

pared to those with relapsed AML (74%; 95% CI: 62-88 *vs*. 44%; 95% CI: 21-92 and 60%; 95% CI: 46-76 *vs*. 22%; 95% CI: 7-75, respectively; *P*=0.008) (Figure 2D).

Multivariable analysis showed that worse ELN 2022 score and relapsed AML following were associated with increased mortality: HR=2.58; 95% CI: 1.2-5.6; *P*=0.02 and HR=2.65; 95% CI: 1.1-6.6; *P*=0.04), respectively). Conversely, ATG and higher albumin (per 1 g/dL) were associated with lower mortality: HR=0.32; 95% CI: 0.1-0.9; *P*=0.03) and HR=0.9; 95% CI: 0.8-0.99; *P*=0.044), respectively). The model discriminated well (C-index =0.745) and met proportional hazards assumptions.

Based on the multivariable Cox model, we derived a patient-level OS risk score as the model's linear predictor and then grouped patients by tertiles of this score into low, intermediate, and high risk. The following equation was used:

Risk score (linear predictor) = 0.948×(ELN step) + 0.975×(Relapse=1, Primary-refractory=0) − 1.139×(ATG Yes=1, No=0) - 0.117×(Albumin in g/dL).

Kaplan-Meier curves demonstrated clear separation across the three groups. Median OS was not reached in the low-risk group (not reached [NR]), 32.9 months (95% CI: 1.2-63.8) in the intermediate-risk group, and 2.1 months (95% CI: 0.3-6.5) in the high-risk group; *P*<0.001 (*Online Supplementary Figure S1*).

Comparative survival analysis with external relapsed/refractory cohorts

In the composite Kaplan-Meier panel, the HCT cohort of primary-refractory AML patients aged ≥70 showed early and durable separation from the non-HCT comparators (*Online Supplementary Figure S2*). The Ven-combination cohort from Park *et al*. comprised relapsed/refractory AML (median age 69 years; 37% ≥70 years; 57% primary-refractory in the Ven arm) treated mainly with Ven + azacitidine ± FLT3/IDH inhibitors; after ranking our cohort to match sex and ELN distributions, the approximate HR favored sequential therapy approach (HR=0.52 *vs*. Ven-combination and HR=0.33 *vs*. the HCT-censored Ven curve). We then compared our cohort to the 10-day decitabine comparators (Ritchie *et al.*: median age 70 years; Bouligny *et al*.: median age 67.5 years; ELN intermediate 53%, adverse 44%). Relative to the 10-day decitabine salvage approach, the sequential therapy cohort showed a lower hazard of death (HR=0.38 *vs*. decitabine).

Discussion

In this single-center study we evaluated a sequential therapy platform (FITCy protocol) prior to allogeneic HCT in patients aged ≥70 years with active AML, mostly primary-refractory. We showed that early disease control was frequent (day +30 CR 82% by ITT; 95.5% among day +30 survivors), with a relative short time to engraftment (neutrophils/platelets at 11/18 days), and complete donor chimerism by day +30 was common. Acute and chronic GVHD were in the expected range for PBSC-RIC HCT. However, NRM clustered early (26% by day 90 and 36% at 3 years) and was largely associated with infections. Three-year GRFS and OS were at the range of 30% and were stratified by a parsimonious multivariable model (ELN 2022 risk, relapse *vs*. primary-refractory, ATG use, albumin), with a clear separation of three Kaplan-Mayer curves groups. Together, these data support the biological premise of sequential therapy in elderly patients with chemo-resistant disease. The concept is coherent with the original FLAMSA experience showing feasibility and long-term survival in younger patients with refractory AML, and with later sequential backbones that reproduce these features in poor-risk settings.[12]

Randomized evidence now suggests that delaying HCT to achieve CR may be unnecessary in refractory or relapsed AML. In the phase III ASAP trial, an "immediate HCT" strategy after brief disease-control measures was non-inferior to salvage induction followed by HCT, reinforcing approaches that compress cytoreduction and move directly to the curative modality.[18] Nevertheless, median age in ASAP was 61 years and while the study supports proceeding rapidly to transplant in fit adults, many septuagenarians are not eligible to myeloablative conditioning and face higher transplant-related toxicity, so sequential reduced-intensity platforms tailored to older adults offer a safer and pragmatic path to curative therapy. In our exploratory overlays, the ≥70 years primary-refractory HCT cohort separated early and durably from non-HCT comparators both when compared to a Ven-combination salvage series[15] (HR=0.52 *vs*. Ven-combination) or when compared to a 10-day decitabine comparators (HR=0.38), consistent with reported refractory or relapsed outcomes on hypomethylating agent schedules where CR/CRi rates are modest and median OS typically 4-6 months.[14,16] Although baseline alignment was achieved for ELN risk and sex (weighted matching), our sequential therapy cohort was older and composed exclusively of primary-refractory patients, whereas external series included both relapsed and refractory cases. Consequently, the observed survival advantage of HCT should be interpreted with caution.

Other retrospective studies reinforces the same message in older adults: Ven-based salvage produces responses but median OS is generally short (4-7 months) outside of successful bridging to HCT, and post-Ven failure outcomes are particularly poor, underscoring that, for fit septuagenarians with active AML, curative intent remains closely tied to timely transplantation rather than prolonged non-transplant salvage.[15,19]

Against this backdrop, toxicity profiles in the elderly are non-trivial: In an EBMT ALWP analysis of AML not in remission (N=360; median age 72 years), 2-year NRM varied by donor and ranged from 17.5-43.9%, while GRFS ranged from 19-35%.[20] Earlier work in the elderly reported 2-year

chronic GVHD near 36-40% under RIC.[21] Against those benchmarks, our acute GVHD (day-200 overall 39.2%; grade 3-4 5.9%) and chronic GVHD (overall 40%; moderate-severe 29%) sit within elderly RIC ranges; our 1- and 3-year NRM are comparable to outcomes reported for non-remission disease with unrelated donors at this age, suggesting that case-mix (active disease, matched unrealted donoar predominance, PBSC source) is a principal driver rather than regimen idiosyncrasy.[22]

Majority of NRM cases occurred in the first 90 days and many cases were associated with infections. Although this observation is based on a relatively small subgroup within the cohort, a non-neutropenic state prior to conditioning was associated with a lower rate of infections. There are several options to improve this domain. First, modifying GVHD prophylaxis to post-transplant cyclophosphamide strategy, based on BMT CTN 1703, may result in superior GRFS, lower steroid exposure and mucosal injury, thereby cutting serious infections, the dominant pattern in our early NRM.[23] Second, Cytomegalovirus prevention with letermovir, should be standardized.[24] We have started to use standard letermovir prophylaxis only in 2023. Presumably, with generalization of the use of letermovir and perhaps also with the extending of the treatment beyond day 100, may be a reasonable default for septuagenarians. Third, antifungal prophylaxis should be tuned in cases of prolong cytopenia and when anticipating steroid exposure.[25]

Based on the mutivaraible analysis for OS we developed a risk model, which is clinically intuitive and may help tailor the platform. ELN 2022 risk group integrates genomic risk; disease status (relapse *vs*. primary-refractory) showed consistently in our cohort impact on outcome; ATG plausibly mitigates chronic GVHD and improves GRFS/OS; and hypoalbuminemia captures frailty and infection susceptibility. Given the observed early infectious NRM, prioritizing the current FITCy-sequential approach for low- and intermediate-risk strata is reasonable while we iterate safety features in the high-risk tertile. To raise results in that high-risk group, two parallel tracks are sensible. One is to make the platform safer with possible adoption of PTCy-based GVHD prophylaxis and rigorous infection control. In this context, and based on emerging clinical data, further reduction of post-transplant cyclophosphamide dosing in older adults may be feasible and safe. Given the limited prospective evidence in this age group, careful dose optimization in future studies will be important to define the minimal effective PTCy intensity that maintains GVHD control while reducing toxicity.

The other is to enhance efficacy without adding substantial toxicity: embed measurable residual disease and early chimerism monitoring with pre-emptive immunomodulation triggers (IST taper and donor lymphocyte infusion) when day +30 to +60 donor chimerism is low or MRD is positive, and deploy molecularly targeted maintenance in appropriate subsets (e.g., FLT3 or IDH inhibitor maintenance). These measures are compatible with the sequential paradigm and directly address the two dominant failure modes - early infection-related NRM and later relapse.

Our study is limited by several factors. First, this is a retrospective, single-center design and modest sample size; second, some endpoints (e.g., acute/chronic GVHD and relapse) had limited events for multivariable modeling, increasing type II error risk. Supportive-care practices and ATG use may have evolved during the study period, and our exploratory overlays *versus* non-HCT comparators, despite raking on ELN and sex, remain ecological rather than fully adjusted. The risk model we presented is internally derived and requires external calibration and validation of cut points across centers, donor sources, and supportive-care eras. Nonetheless, the consistency of core signals (rapid early CR, manageable GVHD, and clean model-based survival separation) and their biological coherence argue for pragmatic adoption with concurrent optimization.

In conclusion, in carefully selected septuagenarians with active AML, a sequential FITCy platform can compress cytoreduction, expedite access to the curative modality, and harness graft-*versus*-leukemia while maintaining GVHD and quality of life at acceptable levels. NRM has remained a significant domain and may require further future modifications in protocol. Prospective, multi-center work comparing sequential backbones (including treosulfan-anchored variants), hard-wiring contemporary infection prevention, and validating the OS risk score should clarify optimal patient selection and consolidate gains in this growing population.

Disclosures

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Contributions

OA, GF, and RR conceived the study, collected and interpreted the data, and drafted the manuscript. OA, GF, YM, IO, YS, DT, CK, IA, and RR contributed to the analysis, reviewed all sections critically, and approved the final version of the manuscript.

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Data-sharing statement

Original data and protocol are available upon request.

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