ARTICLE - Hematopoietic cell transplantation

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

Odelia Amit,[1*] Gil Fridberg,[1*] Yakir Moshe,[1] Inna Ospovat,[2] Yehonatan Sherf,[3] Dina Tshernichovsky,[1] Chen Karni,[1] Irit Avivi[1] and Ron Ram[1]

[1]Bone Marrow Transplantation Unit, Tel Aviv Sourasky Medical Center and Gray School of Medical Sciences, Tel Aviv University, Tel Aviv; [2]Radiation Unit, Oncology Department, Tel Aviv Medical Center and Gray School of Medical Sciences, Tel Aviv University, Tel Aviv and [3]Hematology Department, Soroka University Medical Center, Affiliated to Ben Gurion University of the Negev, Faculty of Health Sciences, Be'er Sheva, Israel

**OA and GF contributed equally as first authors.*

Correspondence: R. Ram
ronr@tlvmc.gov.il

Received: November 7, 2025.
Accepted: December 31, 2025.
Early view: January 22, 2026.

https://doi.org/10.3324/haematol.2025.300184

Methods

Donor Search

Blood for HLA typing was obtained from each patient upon starting induction treatment. High-resolution molecular typing using polymerase chain reaction (PCR) in the sampled DNA with sequence-specific primers was performed for HLA A, B, and C as well as for class II alleles (HLA DRB1 and DQB1). In the case of potential matched siblings, the goal was to achieve HLA results by day 14 after starting induction chemotherapy and at least low/ intermediate resolution for unrelated donor search results by day 21. In addition, the "Donor Search Centre" was notified once the patient was identified as having a "probably refractory disease" according to suggestive findings in the day 14 marrow (if patients received 7+3) or day 21 marrow (in case received VEN-AZA), unrecovered blood count by day 28, or evidence of progression early during treatment. This notification was done to shorten donor identification time in cases no results were finalized by 14-21 days. In specific cases when donor clearance has not finalized, patients could have started the first block prior to full clearance, but were given the second block only after full clearance of the donor was approved.

Treatment

The FITCy protocol is a modified version of the FLAMSA protocol, essentially omitting amsacrine. In detail, patients were initially treated with fludarabine (30 mg/m2/d) and cytarabine (2 g/m2/d <65 years or 1 g/m2/d if ≥ 65 years) for 5 consecutive days from day -13 to day -9. This block was followed by a 3-day break. The RIC part was based on 2 Gy twice daily TBI (day -5) and cyclophosphamide (40 mg/kg/d in case of a matched related donor and 60 mg/kg/d in case of a matched unrelated donor) from day -4 to day -3. In cases of haplo-identical donor, the pre-transplant cyclophosphamide dose was reduced to 25.5 mg/kg/d and post-transplant cyclophosphamide 14.5 mg/kg/d was administered on days +3 and +4. Anti-thymocyte globulin, ATG (Grafalon, Neovii) was given at 5 mg/kg BW/d for both matched siblings and unrelated donors (the protocol was amended on January 2018 to include ATG for all patients after interim analysis showed a high rate of GVHD). Venetoclax was added for the first 12 days of preparative regimen since January 2020 to increase efficacy. As a graft source,

G-CSF mobilized peripheral blood stem cells (PBMC) were preferred and bone marrow (BM) was accepted at the donor's preference. No graft manipulation was performed.

Supportive care

All patients were hospitalized in a designated ward in single-bed rooms equipped with HEPA filters. All patients receiving FITCy were given prophylaxis with ciprofloxacin. Antifungal prophylaxis consisted of posaconazole (300 mg/d) or voriconazole (200 mg, twice daily) and HSV/VZV prophylaxis of valacyclovir (1000 mg/d) or acyclovir (1600 mg/d). Pneumocystis jirovecii prophylaxis consisted with co-trimoxazole 3 days per week. Since 2023, all CMV-pos patients were given letermovir. Weekly monitoring of peripheral blood CMV-DNA by PCR was performed. In case of CMV reactivation, valganciclovir or intravenous ganciclovir treatment was initiated. During the period of neutropenia, a weekly monitoring of galactomannan antigen in the peripheral blood was performed. Prophylaxis of graft versus host disease (GvHD) consisted of cyclosporine A (CsA, given from day −1 to +100 adjusted to serum level (200–350 ng/ml), tapered from day +100 and discontinued up to day +180, if no signs of GvHD were present and mycophenolate mofetil (MMF, 2 g/day in matched related donors and 3 gr/day in unrelated donors given from day 0 to +30, tapered from day +30 and discontinued from day +50). In case of CsA side effects or non-tolerability, CsA was replaced by tacrolimus adjusted to serum level (5-15 ng/ml). During hospitalization, clinical status, adverse events, haematological as well as biochemistry parameters were monitored on a daily basis. After discharge, patients were followed in the outpatient clinic at least twice per week until day +60 with gradually longer intervals thereafter. Regimen-related toxicities were graded according to the CTCAE 5.0. Acute and chronic GvHD were graded and staged by the standard MAGIC and NIH criteria, respectively.(1, 2)

Evaluation of disease and response

Since majority of patients had refractory disease, the disease stage and time-from-diagnosis components of the AL-EBMT score were not applicable.(3)We therefore calculated a modified score including four domains: age (70–74 vs. ≥75 years), Karnofsky performance status, donor

type, and female-to-male donor–recipient mismatch. Each adverse factor was assigned 1 point (range 0–4), and patients were categorized as low risk (0–1) or high risk (2–4).

Engraftment was defined as the first of 3 days with a neutrophil count of more than 0.5×10^9/L and a non-transfused platelet count of more than 20×10^9/L. Disease response and donor whole marrow chimerism were assessed at day +30 and day +100 in BM. Complete remission (CR) was defined as less than 5% blast cells in BM by cytomorphology and flow-cytometry, and neutrophils of more than 1500/μL. Hematologic relapse was defined by the reappearance of blast cells in the PB, or by more than 5% blast cells in BM. Death from leukemia was defined as death with refractory disease after transplantation or death from any cause after post-transplantation relapse. Non-relapse mortality (NRM) was defined as death from any cause other than refractory disease or relapse. GVHD–relapse–free survival (GRFS) was defined as the time from transplantation to the first occurrence of grade III–IV acute GVHD, systemic therapy–requiring chronic GVHD, relapse, or death from any cause, whichever occurred first.

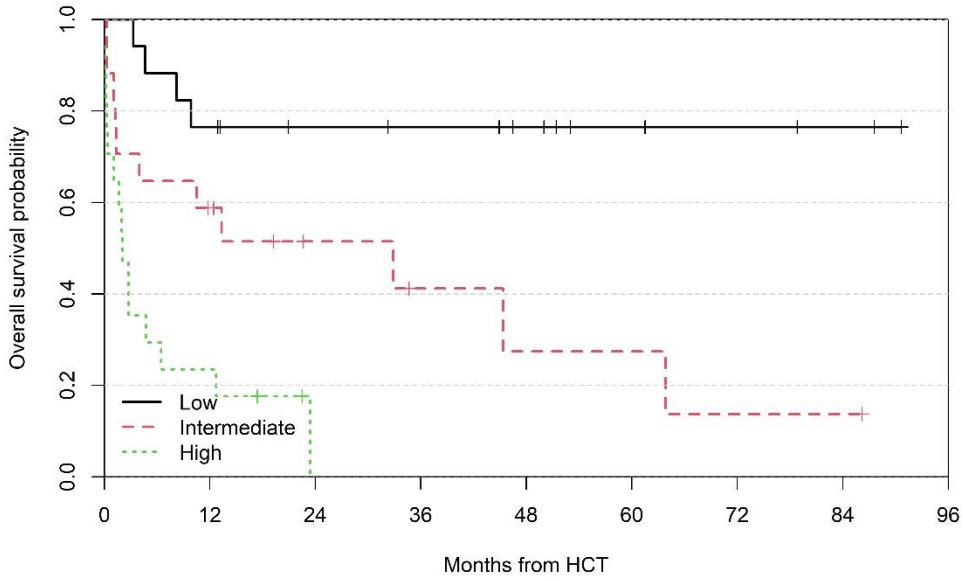
Because no randomized studies have evaluated HCT in elderly patients with primary refractory AML, survival was benchmarked against contemporary non-transplant salvage cohorts reported in comparable age groups and disease settings. Three published cohorts were selected for comparison: Park et al.(4) - 88 patients with relapsed/refractory AML (median age 69 years; 37% ≥ 70) treated with venetoclax + azacitidine ± FLT3/IDH inhibitors or intensive chemotherapy; Bouligny et al. (5) - AML treated with a 10-day decitabine regimen (mixed upfront and relapsed settings; median age 67.5 years); and Ritchie et al. (6) - 102 relapsed/refractory AML patients treated with repeated 10-day decitabine cycles (median age for the salvage subset not reported).

Legends

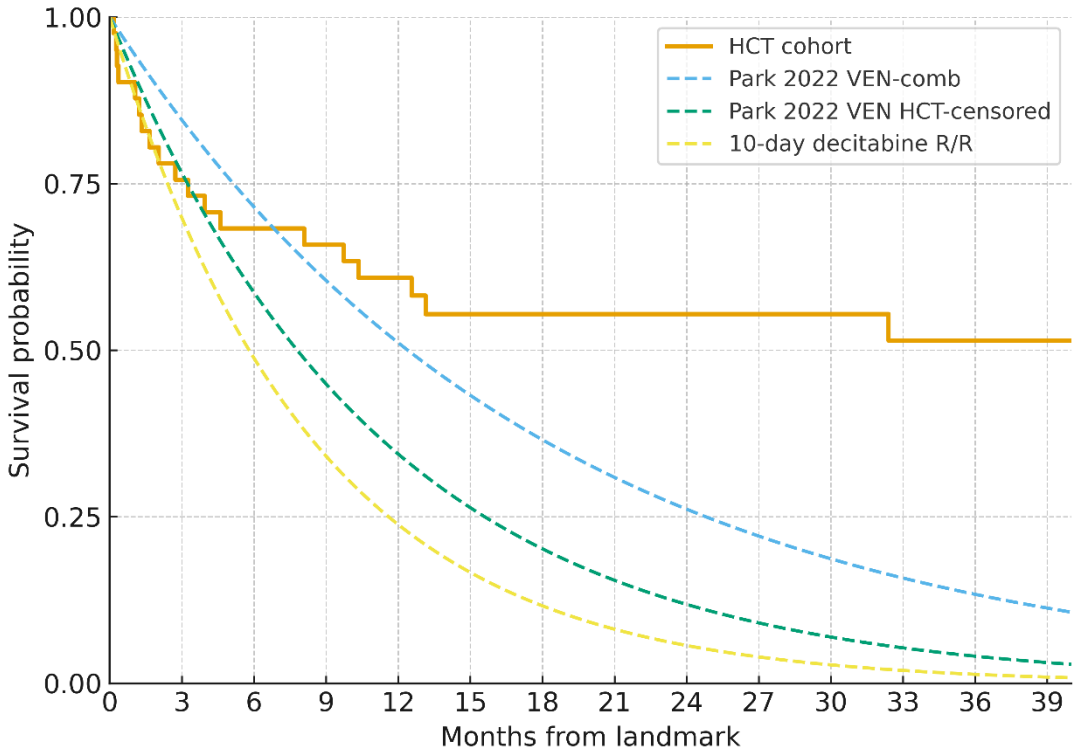
Supplemental Figure 1 - OS According to Multivariable Risk Score

Supplemental Figure 2 - Kaplan–Meier comparison: Patients with primary refractory AML who received sequential therapy vs heuristic comparators (exponential medians)

Supplemental Figure 1



Supplemental Figure S2



References

1. Harris AC, Young R, Devine S, Hogan WJ, Ayuk F, Bunworasate U, et al. International, Multicenter Standardization of Acute Graft-versus-Host Disease Clinical Data Collection: A Report from the Mount Sinai Acute GVHD International Consortium. Biol Blood Marrow Transplant. 2016 Jan;22(1):4-10.
2. Jagasia MH, Greinix HT, Arora M, Williams KM, Wolff D, Cowen EW, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report. Biol Blood Marrow Transplant. 2015 Mar;21(3):389-401 e1.
3. Shouval R, Bonifazi F, Fein J, Boschini C, Oldani E, Labopin M, et al. Validation of the acute leukemia-EBMT score for prediction of mortality following allogeneic stem cell transplantation in a multi-center GITMO cohort. Am J Hematol. 2017 May;92(5):429-34.
4. Park S, Kwag D, Kim TY, Lee JH, Lee JY, Min GJ, et al. A retrospective comparison of salvage intensive chemotherapy versus venetoclax-combined regimen in patients with relapsed/refractory acute myeloid leukemia (AML). Ther Adv Hematol. 2022;13:20406207221081637.
5. Bouligny IM, Mehta V, Isom S, Ellis LR, Bhave RR, Howard DS, et al. Efficacy of 10-day decitabine in acute myeloid leukemia. Leuk Res. 2021 Apr;103:106524.
6. Ritchie EK, Feldman EJ, Christos PJ, Rohan SD, Lagassa CB, Ippoliti C, et al. Decitabine in patients with newly diagnosed and relapsed acute myeloid leukemia. Leuk Lymphoma. 2013 Sep;54(9):2003-7.