NORTHSIDE HOSPITAL CANCER INSTITUTE
LEUKEMIA PROGRAM

LEUKEMIA NEWS

Winter 2020 Edition

In This Issue

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Early Referral to a Combined Leukemia/ Transplant Program Improves Outcomes for Older Acute Myeloid Leukemia (AML) Patients

By: Scott Solomon, MD

Acute myeloid leukemia (AML) is generally a disease of older adults. The median age at diagnosis is 68 years, with patients diagnosed most frequently between ages 65 and 74 years. For younger AML patients, current treatment guidelines recommend intensive chemotherapy (IC) with an anthracycline and cytarabine in order to achieve remission induction. This is followed by curative-intent post-remission therapy, which can vary from chemotherapy alone for favorable-risk AML to allogeneic hematopoietic cell transplant (HCT) for poor-risk patients. Such an approach can lead to long-term disease control in approximately 40–50% of younger adult AML patients.

Older AML patients (≥60 years of age) have significantly worse outcomes, and the optimal approach to treatment for these patients remains less clear. Older AML patients have higher risk disease characteristics, including less favorable cytogenetics and molecular findings, as well as a higher incidence of drug resistance. Advanced age can also be accompanied by comorbidities and frailty, which may have an important impact on tolerance to intensive therapies. However, studies show that age is more likely to be a surrogate for these other risk factors; and therefore, age alone is not a reliable variable to determine treatment or predict outcome.

Due to a perceived intolerance, many older AML patients do not receive therapy, and few are considered for curative intent HCT. This occurs despite the fact that multiple studies have now confirmed the efficacy of treatment vs palliative approaches in improving outcomes for elderly AML patients.[1-3] A recent study documenting treatment patterns in the US, utilizing the linked Surveillance, Epidemiology, and End Results (SEER)-Medicare database, demonstrated that 48% of AML patients 66−80 years of age receive no treatment for their disease. Even more striking is the infrequent use of HCT, which is utilized in only 6% of AML patients between 66 and 75 years of age.[2]

At the combined Leukemia/Transplant Program at Northside Hospital Cancer Institute (NHCI), our treatment approach aims to deliver remission induction therapy to most older AML patients referred to our program regardless of age, with the goal of transplanting patients with intermediate- or poor-risk disease, when feasible. In order to better understand the real-world outcomes that can be achieved when treating older AML patients with curative intent, we recently analyzed 323 consecutive AML patients (≥60 years) referred to the NHCI Leukemia/ Transplant Program from 2009 to 2017.[4] This population represented an unselected group of older AML patients with a median age of 70 years (range, 60-88 years) and mostly higher-risk disease (poor-risk 50%, intermediate-risk 35%, favorable-risk 15%).

Induction chemotherapy with the intent of achieving remission was given to 81% of patients (IC 63%, hypomethylating agent [HMA] 18%). Sixty percent of treated patients ultimately achieved remission, with half of these patients surviving at least 2 years. At the start of induction chemotherapy, a search for a transplant donor was initiated in all transplant-eligible patients (age 60-75 years with non–favorable-risk disease) in order to establish a suitable donor for transplant (HLA-matched related, HLA-matched unrelated or haploidentical family member) once remission was achieved. In our analysis, almost half (46%) of transplant-eligible patients ultimately received a transplant in first remission. Transplanted patients had significantly improved 2- and 3-year survival rates of 59% and 40%, respectively, compared with 26% and 18%, respectively, in non-transplanted patients; these findings remained significant in a time-dependent Cox multivariate analysis (HR 0.59, p=0.023). Furthermore, older AML patients with favorable-risk

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disease, although representing only 15% of cases, had particularly good outcomes without the need for transplant: 81% achieved remission, and 58% survived at least 2 years.

This published experience of 323 consecutive, elderly AML patients referred for evaluation and treatment suggests that survival can be improved through a coordinated approach of remission induction therapy followed by HCT when feasible. Because of our commitment to achieving remission, 81% of patients received induction treatment, with nonresponding patients offered reinduction chemotherapy, when feasible. With this approach, 60% of treated elderly AML patients ultimately achieved remission, with approximately half of these surviving 2 years. Furthermore, the integrated nature of our Leukemia/HCT program coupled with the use of alternative donors allowed for a 46% rate of HCT utilization for transplant-eligible patients achieving remission to induction therapy. This rate compares favorably to the 14% rate of HCT seen in a previously published prospective feasibility analysis of similar patients from MD Anderson Cancer Center.[5] As observed in other published studies, transplanted elderly AML patients in our study enjoyed a favorable 2- and 3-year post-remission survival probability of 59% and 40%, respectively. Such data add to a growing body of literature suggesting that a significant proportion of elderly AML patients benefit from a curative intent treatment approach. Therefore, referral to a comprehensive Leukemia/HCT specialty center is appropriate for most elderly AML patients up to 80 years of age.

1. Juliusson G. *Clin Lymphoma Myeloma Leuk*. 2011;11:S54-S59.
2. Medeiros BC, et al. *Ann Hematol*. 2015;94:1127-1138.
3. Oran B, et al. *Haematologica.* 2012;97:1916-1924.
4. Solomon SR, et al. *Bone Marrow Transplant*. 2020;55:189-198.
5. Estey E, et al. *Blood*. 2007;109:1395-400.

NSH1238: A Phase 1b Study of SEL120 in Patients with Acute Myeloid Leukemia or High-Risk Myelodysplastic Syndrome

This is an open-label, multi-center, modified 3+3 dose escalation study designed to establish the recommended dose for further clinical development. This first-in-human study will evaluate the recommended dose and safety of SEL120 given as monotherapy over a range of dose levels, following a closely controlled dose escalation study design.

SEL120 is a novel small molecule, selective CDK8/19 inhibitor, for the treatment of AML and HRMDS. SEL120 has demonstrated strong efficacy in pre-clinical AML models, and pre-clinical experiments have revealed the potential of selectively eradicating leukemia cells, including cells with leukemic stem cell characteristics whilst sparing normal hematopoietic cells. This mechanism of action offers a new opportunity for a personalized and potent treatment approach for AML and HRMDS.

ELIGIBILITY CRITERIA

1. Adults ≥18 years of age with:
   - R/R AML: received no more than 3 prior lines of therapy and with no available therapy
   - R/R HRMDS: received no more than 3 prior lines of therapy and with no available therapy
2. ECOG PS 0-2
3. No anti-cancer treatment within previous 2 weeks (hydrea exempt)
4. Life expectancy ≥12 weeks
5. Prior HSCT allowed; must be >120 prior to study drug dosing

EXCLUSION CRITERIA

1. Previous treatment with CDK8-targeted therapy
2. aGVHD ≥grade 2, active moderate-to-severe cGVHD, or requiring systemic immunosuppressive therapy
3. Patients with personal or family history of serious ventricular arrhythmia, or QTcB ≥450ms

TREATMENT PLAN

Doses of SEL120 will be administered as a single oral dose every other day for a total of 7 doses (i.e., on Days 1, 3, 5, 7, 9, 11, and 13 in a 3-week treatment cycle). The first dose between the first 2 patients in any dose cohort enrolling more than 1 patient must be separated by a minimum of 48 hours.

Up to 8 cohorts of 1 to 6 patients will be evaluated to assess dose levels ranging from 10 to 225 mg.

Patients will receive SEL120 until disease progression, intolerable toxicity, or withdrawal of consent.

NSH C374: A Phase III Randomized, Double-Blind Trial to Evaluate the Efficacy of Uproleselan (GMI-1271) Administered with Chemotherapy versus Chemotherapy Alone in Patients with Relapsed/Refractory Acute Myeloid Leukemia

This is a multi-center, randomized, double-blind trial in adults with relapsed/refractory AML. This trial will enroll approximately 380 randomized adult subjects with primary refractory AML or relapsed AML and eligible to receive induction chemotherapy.

Uproleselan is a synthetic glycomimetic designed to inhibit binding of cells to E-selectin. E-selectin is expressed transiently in the normal vasculature during an inflammatory response and constitutively in the bone marrow. Increased expression of E-selectin, as seen in inflammatory conditions, malignant states such as leukemia, and during chemotherapy, is associated with increased shedding of E-selectin from the cell surface. AML blast cells bound to E-selectin are resistant to the effects of chemotherapy. E-selectin inhibition by uproleselan disrupts the adhesion of AML cells in bone marrow and can mobilize AML blasts out of the bone marrow into the blood stream.

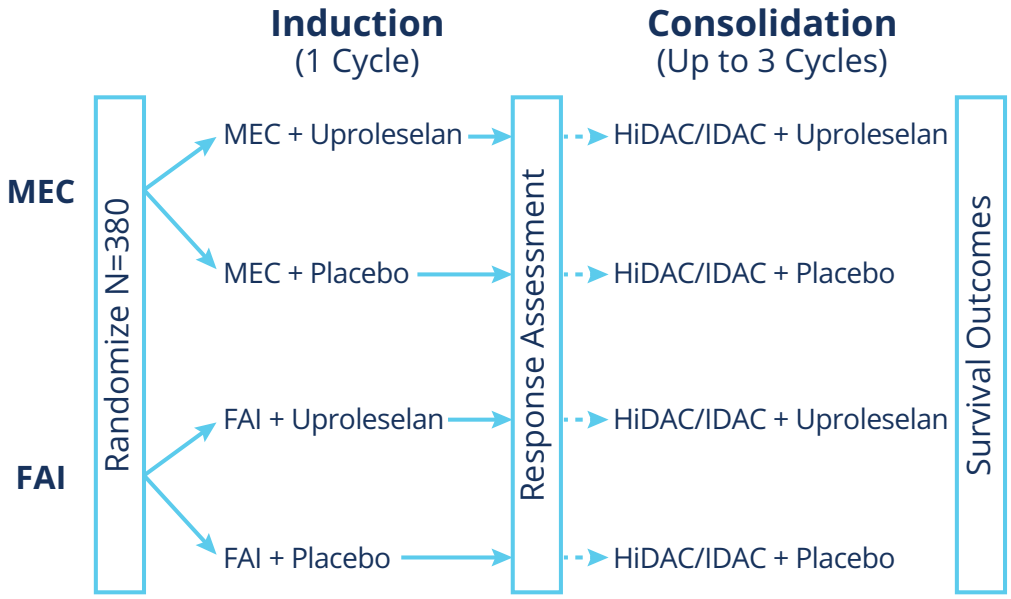
ELIGIBILITY CRITERIA

1. Adults 18-75 years of age with:
   - AML diagnosis (>20% myeloid blasts) at time of initial diagnosis
   - Primary refractory AML
     - Received only 1 cycle of induction containing anthracycline and cytarabine
   - Relapsed AML
     - First or second untreated relapse
2. ECOG PS 0-2
3. Prior HSCT allowed; must be >4 months prior to study drug dosing

EXCLUSION CRITERIA

1. Secondary refractory excluded
2. aGVHD ≥grade 2 or active cGVHD requiring therapy

TREATMENT PLAN



Subjects will be randomized 1:1 to receive either uproleselan or placebo in a blinded fashion administered together with chemotherapy. Backbone induction chemotherapy will be the investigator's choice of either MEC or FAI. Consolidation therapy will be with cytarabine.

- MEC = combination regimen of mitoxantrone, etoposide, and cytarabine
- FAI = combination regimen of fludarabine, cytarabine, and idarubicin
- HiDAC = high-dose cytarabine
- IDAC = intermediate-dose cytarabine

Randomized subjects will receive a sentinel dose of uproleselan or placebo 24 hours prior to the first dose of chemotherapy in each treatment cycle, then a dose every 12 hours throughout the chemotherapy treatment and for the 2 days following the last dose of chemotherapy.

Each dose of uproleselan will be a fixed dose of 800 mg. Uproleselan or placebo will be administered IV at a steady rate over a 20-minute period. Backbone induction chemotherapy is given over 5 days. Consolidation therapy can be given up to 3 cycles and will be administered over 5 days of each cycle.

CAR T-cell Clinical Research Trials Available for Multiple Myeloma, Non-Hodgkin's Lymphoma, Small Lymphocytic Lymphoma and Chronic Lymphocytic Leukemia

Disease	Trial Number	Name of Trial	Drug & NCT Identifier
CLL/Small Lymphocytic Lymphoma	**NSH1226**	An Open-Label, Phase 1 Safety and Phase 2 Randomized Study of JCAR017 in Subjects with Relapsed or Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma **Inclusion Criteria** • Age ≥ 18 • ECOG PS ≤ 1 • CLL with clinically measurable disease • SLL with clinically measurable disease **Exclusion Criteria** • Known active CNS disease • History of another primary malignancy <2 yrs • Richter's transformation	JCAR017 NCT03331198
Multiple Myeloma	**NSH1216**	A Phase 3, Multicenter, Randomized, Open-Label Study to Compare the Efficacy and Safety of bb2121 versus Standard Triplet Regimens in Subjects with Relapsed and Refractory Multiple Myeloma (rrMM) (KarMMa-3) **Inclusion Criteria** • Age ≥ 18 • ECOG PS 0 or 1 • Received 2 - 4 prior MM regimens • Received prior treatment with daratumumab, a proteasome inhibitor and an immunomodulatory compound containing regimen for at least 2 consecutive cycles • Refractory to the last treatment regimen • Achieved at least a minimal response to at least 1 prior treatment regimen • Has received and failed Bruton tyrosine kinase inhibitor (BTKi) treatment or is ineligible for BTKi treatment. **Exclusion Criteria** • Active or history of plasma cell leukemia, WM, POEMS syndrome, or amyloidosis • COPD with FEV1 50% of predicted normal • Therapy-based therapeutic for cancer, investigational cellular therapy for cancer, or BCMA targeted therapy • Received an autologous stem cell transplant within 12 wks prior to randomization	bb2121 NCT03651128
NHL	**NSH1170**	A Phase 1, Multicenter, Open-Label Study of JCAR017, CD19-Targeted Chimeric Antigen Receptor (CAR) T-Cells, in Relapsed and Refractory (R/R) B-Cell Non-Hodgkin Lymphoma **Inclusion Criteria** • Age ≥ 18 years • ECOG PS between 0 and 1 • Relapsed or refractory B-cell NHL or Mantle Cell Lymphoma (MCL) • Previous treatment of at least 2 lines of therapy or 1 line in MCL or after auto HSCT • Archived tumor biopsy tissue available from the last relapse and corresponding pathology report available for disease confirmation, and willing to undergo pre- and post-treatment biopsy if at least one tumor-involved site is deemed accessible at time of screening **Exclusion Criteria** • CNS only involvement with malignancy-secondary CNS involvement are allowed on study • Active acute or chronic GVHD • Prior malignancy <2 yrs • Active hepatitis B, hepatitis C, or HIV	JCAR017 NCT02631044
	NSH1207	A Global Randomized, Multicenter Phase 3 Trial to Compare the Efficacy and Safety of JCAR017 to Standard of Care in Adult Subjects with High-Risk, Transplant-Eligible Relapsed or Refractory Aggressive B-Cell Non-Hodgkin Lymphomas (TRANSFORM) **Inclusion Criteria** • Age ≥18 and ≤ 75 at time of consent • ECOG PS ≤ 1 • Relapsed or refractory B-cell NHL • Refractory (SD,PD,PR, or CR with relapse before 3 months) or relapsed (CR with relapse on or after 3 months) within 12 months from CD20 antibody and anthracycline containing first line therapy • Must have PET positive lesion(s) at screening • Enough tumor material must be available for confirmatory by central pathology • Secondary CNS involvement is acceptable **Exclusion Criteria** • Not eligible for HSCT • Previous CD-19 targeted therapy • Planned allo HSCT • Prior malignancy resolved < 2yrs • Treatment with prior gene therapy • History/active hepatitis B, hepatitis C or HIV	JCAR017 NCT03575351
	NSH1230	A Phase 2 Study of Lisocabtagene Maraleucel (JCAR017) as Second-Line Therapy in Adult Patients with Aggressive B-Cell NHL **Inclusion Criteria** • Age ≥ 18 • ECOG PS 0-2 • Diagnosis: – DLBCL NOS or transformed from follicular lymphoma – High grade B-Cell lymphoma with MYC and BCL and/or BCL6 rearrangements with DLBCL histology (double/triple hit lymphoma [DHL/THL]) – Follicular lymphoma Grade 3B • Previous treatment must include single line of chemoimmunotherapy containing an anthracycline and a CD20 targeted agent • Subjects must be deemed ineligible for both high-dose chemotherapy and HSCT while also having adequate organ function for CAR T-cell treatment **Exclusion Criteria** • Subjects with central nervous system (CNS)-only involvement by malignancy (subjects with secondary CNS involvement are allowed on study) • Previous CD-19 targeted therapy and or prior HSCT	JCAR017 NCT03483103

Leukemia Open Clinical Research Trials

Disease	Trial Number	Name of Trial	Drug & NCT Identifier
AML	**NSH1150**	Phase 2 Trial of Lymphodepletion and Anti-PD-1 Blockade to Reduce Relapse in High-Risk AML Patients Who Are Not Eligible for Allogeneic Stem Cell Transplantation	Pembrolizumab NCT02771197
Heme Malignancies	**NSH1164**	A Phase 1 Multiple Dose Study to Evaluate the Safety and Tolerability of XmAb® 14045 in Patients with CD123-Expressing Hematologic Malignancies	XmAB® 14045 NCT02730312
Heme Malignancies	**NSH1208**	A Phase 1 Trial to Evaluate the Potential Impact of Renal Impairment on the Pharmacokinetics and Safety of CPX-351 (Daunorubicin and Cytarabine) Liposome for Injection Treatment in Adult Patients with Hematologic Malignancies	CPX-351 NCT03555955
AML	**NSH1223**	A Phase 1b Dose-Escalation Study to Assess the Safety, Pharmacokinetics, Pharmacodynamics, and Preliminary Efficacy of PLX2853 in Subjects with Relapsed or Refractory Acute Myeloid Leukemia or High-Risk Myelodysplastic Syndrome	PLX2853 NCT03787498
AML/MDS	**NSH1238**	A Phase Ib study of SEL120 in Patients with Acute Myeloid Leukemia and High-Risk Myelodysplastic Syndrome	SEL120 NCT04021368
AML/MDS	**C332**	A Phase I Study of Ipilimumab in Combination with Decitabine in Relapsed or Refractory Myelodysplastic Syndrome/Acute Myeloid Leukemia	Ipilimumab NCT02890329
AML	**C374**	A Phase III Randomized, Double-Blind Trial to Evaluate the Efficacy of Uproleselan Administered with Chemotherapy vs Chemotherapy Alone in Patients with Relapsed/Refractory AML	Uproleselan (GMI-1271) NCT03616470

NEED RETURN ADDRESS

Referrals

- For urgent acute leukemia referrals, a physician is available by phone 24 hours a day, 7 days a week at (404) 255-1930
- For routine outpatient referrals/consults or questions, please contact our leukemia coordinators at (404) 255-1930
- To find out more about our clinical trials, please contact Stacey Brown at (404) 780-7965 or stacey.brown@northside.com

Visit http://www.northside.com/leukemia and/or BMTGA.com for more information and news

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