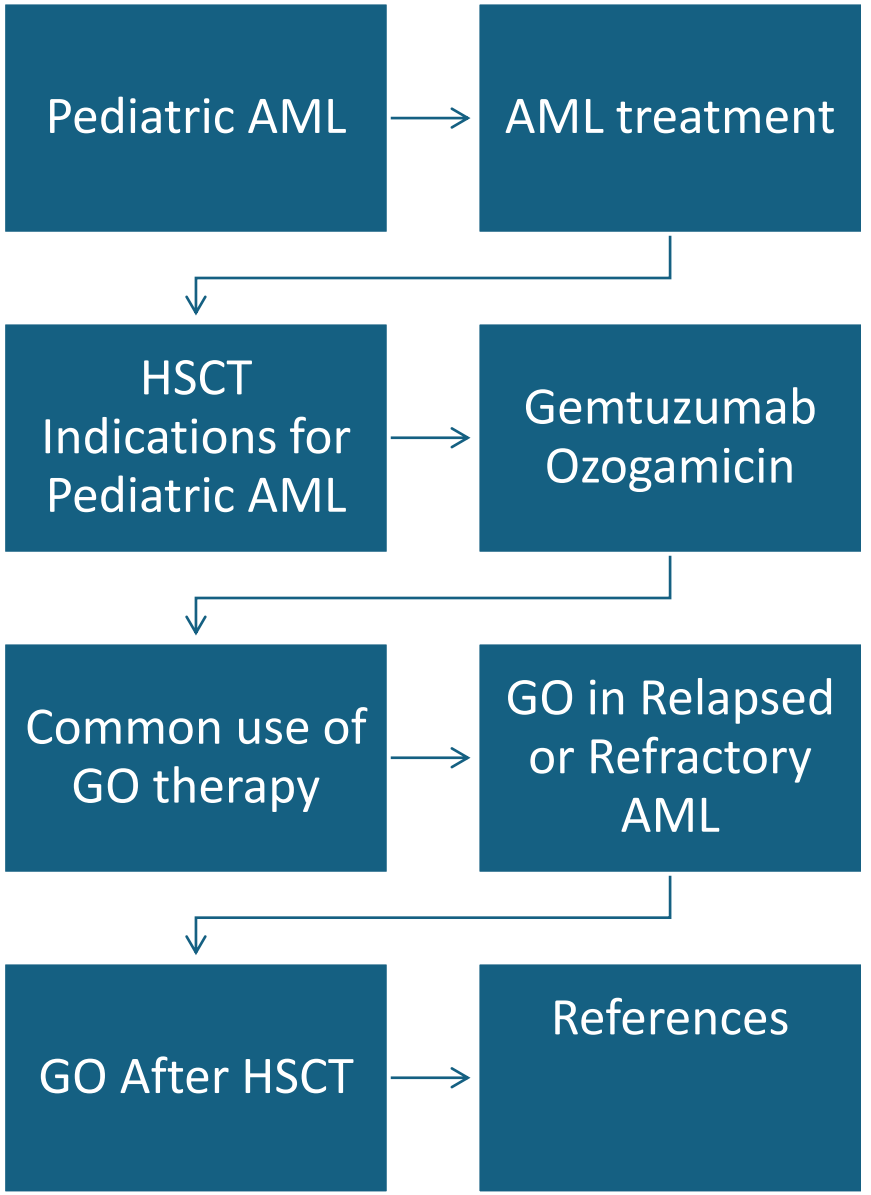
Gemtuzumab Ozogamicin and Pediatric HSCT

Amir Ali Hamidieh, M.D.
Professor of Pediatric Hematology/Oncology & Stem Cell Transplant
Director, Pediatric Cell & Gene Therapy Research Center
Tehran University of Medical Sciences
Director, Pediatric Stem Cell Transplant Department
Children's Medical Center
Tehran, Iran

Concept


Pediatric AML
AML treatment
HSCT Indications for Pediatric AML
Gemtuzumab Ozogamicin
Common use of GO therapy
GO in Relapsed or Refractory AML
GO After HSCT
References

Pediatric AML

- Acute myeloid leukemia (AML): a malignancy → of the stem cell precursors of the myeloid lineage (red blood cells, platelets, and white blood cells other than B and T cells)

- AML can arise in patients:
  1. de novo malignancy
  2. Secondary malignancy (underlying hematological disorder or prior to medical therapy)

- AML classification based on prognostic risk:
  1. Favorable
  2. Intermediate
  3. Adverse

AML Treatment

1. Initial induction therapy to achieve complete remission (CR)

2. Post-remission therapy to prevent relapses of the disease

HSCT Indications for Pediatric AML

1. High-Risk (HR) Genetic / Molecular Features:
    - Unfavorable cytogenetics, Monosomy 5 or 7 or 17 / TP53 abnormalities
    - Complex karyotype
    - KMT2A high-risk rearrangements
    - High-risk molecular mutations: FLT3-ITD , WT1 , CEBPA
2. Poor Early Treatment Response
    - High MRD after Induction
3. Relapsed AML
4. Standard risk

HSCT Indications for Pediatric AML with Standard Risk

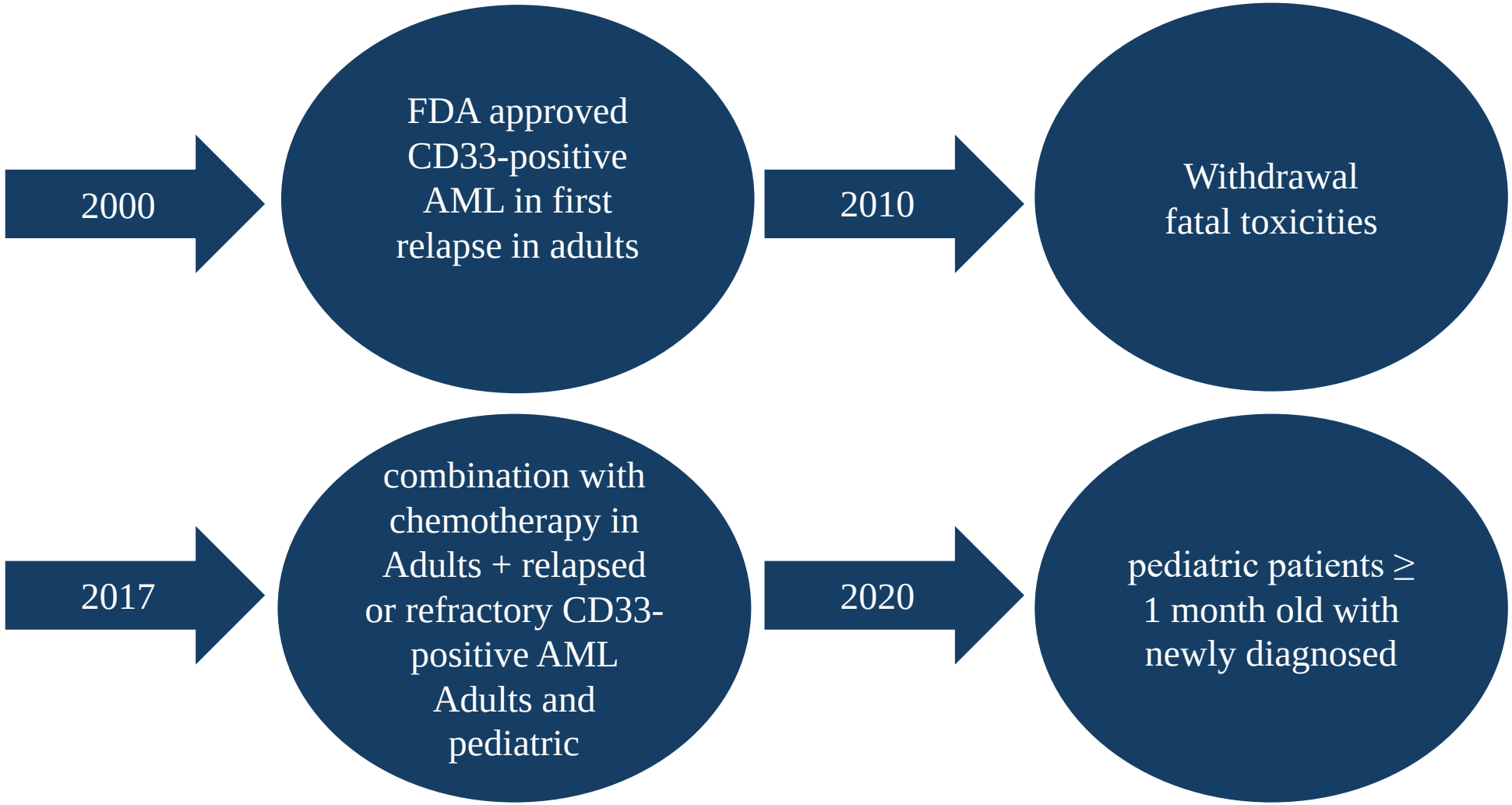
- Standard Risk
  - Absence of known high-risk genetic abnormalities

- According to MRD status:
  1. MRD Negative after induction ⇒ chemotherapy alone
  2. MRD Positive after induction ⇒ HSCT in first complete remission (CR1)

Gemtuzumab Ozogamicin(Mylotarg)

- Gemtuzumab Ozogamicin → A monoclonal antibody, treats AML by targeting CD33
- Ozogamicin:
  - a very powerful antitumor antibiotic
  - derived from calicheamicin
- Calicheamicin:
  - Attached to the minor groove of DNA
  - double-strand breaks
  - cell death

Gemtuzumab Ozogamicin Approval History



European Commission(EC) Approval

In 2018, the European Commission approved GO → in combination with daunorubicin and cytarabine → for patients more than 15 years with previously untreated, de novo, CD33-positive AML

Common use of GO therapy

Newly Diagnosed AML (Frontline Therapy)

Relapsed or Refractory AML

After HSCT

GO in Relapsed or Refractory AML

Original Article

Gemtuzumab Ozogamicin Can Reduce Minimal Residual Disease in Patients With Childhood Acute Myeloid Leukemia

Carol O'Hear, MD, PhD[1,2]; Hiroto Inaba, MD, PhD[1,2]; Stanley Pounds, PhD[3]; Lei Shi, PhD[3]; Gary Dahl, MD[4]; W. Paul Bowman, MD[5]; Jeffrey W. Taub, MD[6]; Ching-Hon Pui, MD[1,2,7]; Raul C. Ribeiro, MD[1,2]; Elaine Coustan-Smith, MS[8]; Dario Campana, MD, PhD[8]; and Jeffrey E. Rubnitz, MD, PhD[1,2]

BACKGROUND: Gemtuzumab ozogamicin (GO) is an active agent for the treatment of CD33-postive acute myeloid leukemia (AML) and may improve the outcome of specific patient subgroups when combined with conventional chemotherapy. However, to the best of the authors' knowledge, the effects of GO on levels of minimal residual disease (MRD) are unknown. **METHODS:** Pediatric patients with AML who received GO, either alone or in combination with chemotherapy on the AML02 multicenter trial, were analyzed to determine the effects of GO on MRD and outcome. **RESULTS:** Among 17 patients who received GO alone because of persistent leukemia, 14 had a reduction in their MRD level and 13 became MRD negative. Of the 29 who received chemotherapy in combination with GO after responding poorly to chemotherapy, 28 demonstrated reduced MRD and 13 became MRD negative. Treatment with GO effectively reduced MRD before hematopoietic stem cell transplantation and was not found to be associated with increased treatment-related mortality after transplantation. **CONCLUSIONS:** GO is effective in reducing MRD levels in pediatric patients with AML and may improve the outcome of those patients at high risk of disease recurrence. *Cancer* 2013;119:4036-43. © *2013 American Cancer Society.*

KEYWORDS: acute myeloid leukemia, minimal residual disease, gemtuzumab ozogamicin, treatment-related mortality.

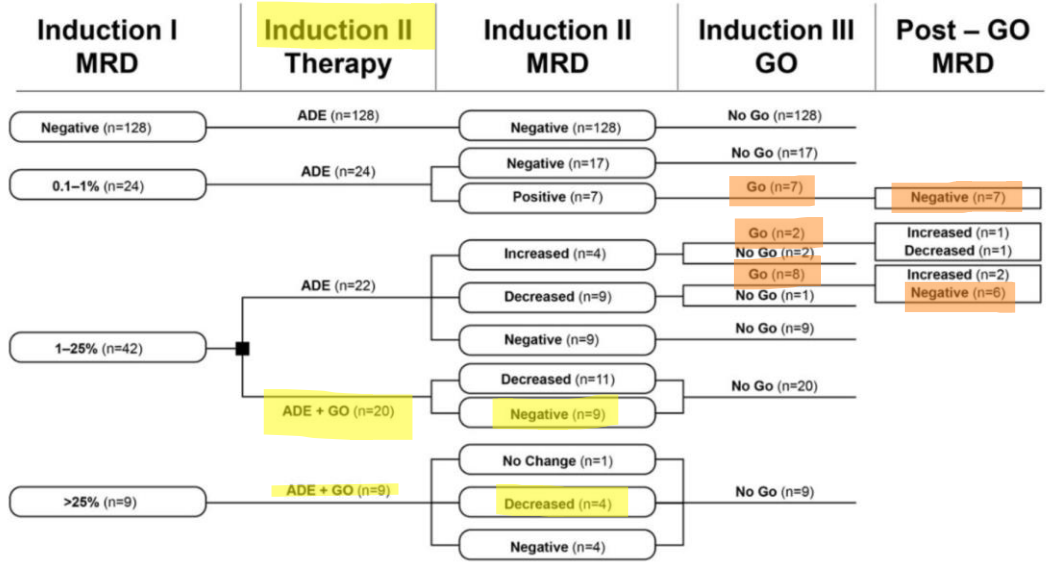


Figure 1. Patient flow chart is shown demonstrating minimal residual disease (MRD) levels and the therapy received. An MRD level ≥ 0.1% was considered positive. "Decreased" indicates that MRD levels were lower, but still positive. ADE indicates cytarabine, daunorubicin, and etoposide; GO, gemtuzumab ozogamicin.

1-25% or >25 % after induction 1

Using 3 mg/m2 of GO + low-dose chemotherapy Induction 2

MRD level ≥ 0.1% after induction 2

6 mg/m2 of GO induction 3

GO in Relapsed or Refractory AML

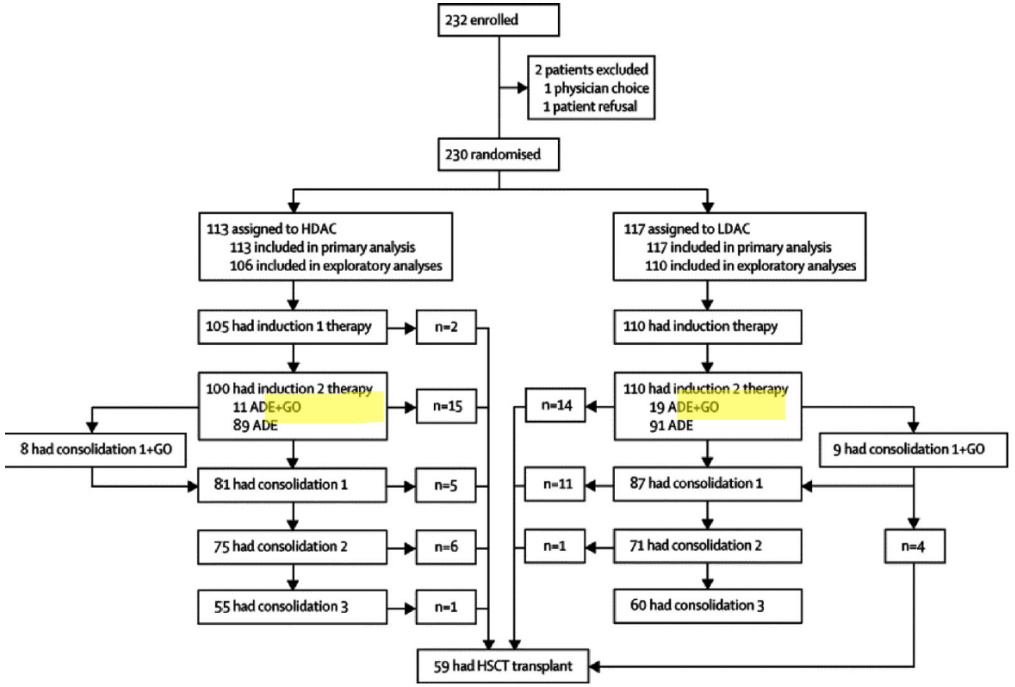
- Patients who underwent HSCT:
  - Group 1: patients who didn't receive GO before HSCT
  - Group 2: which received GO → had significantly higher induction 1 MRD levels
- The group 2 achieved similar MRD levels prior to HSCT because of GO therapy
- Posttransplant OS and EFS rates were similar in the 2 groups
- → Administration of GO in patients, reducing MRD levels before transplant without increasing transplant-related mortality
- Despite it was expected that OS and EFS were lower in group 2

GO in Relapsed or Refractory AML

Residual Disease-Directed Therapy for Childhood Acute Myeloid Leukemia: Results of the AML02 Multicenter Trial

Background—We sought to improve outcome of childhood acute myeloid leukemia (AML) by applying risk-directed therapy based on the genetic abnormalities of the leukemic cells and measurements of minimal residual disease (MRD) as determined by flow cytometry during treatment.

Methods—From October 13, 2002 to June 19, 2008, 232 patients with de novo AML (n=206), therapy- or myelodysplasia-related AML (n=12), or mixed-lineage leukemia (n=14) were enrolled at eight centers. Block, nonblinded randomization, stratified by cytogenetic or morphologic subtype, assigned patients to high-dose (18 g/m^2, n=113) or low-dose (2 g/m^2, n=117) cytarabine (A), given together with daunorubicin (D) and etoposide (E) (Induction I); achievement of MRD negative status was the primary endpoint. Induction II consisted of ADE with or without gemtuzumab ozogamicin (GO); consolidation therapy included three additional courses of chemotherapy or hematopoietic stem cell transplantation (HSCT). Levels of MRD were used to allocate GO and determine the timing of Induction II; both MRD and genetic abnormalities at diagnosis were used to determine final risk classification. Low-risk patients (n=68) received 5 courses of chemotherapy, whereas high-risk patients (n=79), as well as standard-risk patients (n=69) with matched sibling donors, were eligible for HSCT (performed in 48 high and 8 standard-risk patients). All randomized patients (n=230) were analyzed for the primary endpoint. The other analyses were limited to the 216 patients with AML, excluding mixed-lineage leukemia. This trial, closed to accrual, is registered with ClinicalTrial.gov, number NCT00136084.



27 of the 29 evaluable patients who received ADE plus GO had reductions in MRD levels, increasing the chance of achieving remission for HSCT

GO in Relapsed or Refractory AML

Association of fludarabin, cytarabine, and fractioned gemtuzumab followed by hematopoietic stem cell transplantation for first-line refractory acute myeloid leukemia in children: A single-center experience

Mathilde Penel-Page[1,2] | Adriana Plesa[3] | Sandrine Girard[4] | Alice Marceau-Renaut[5] | Cécile Renard[1] | Yves Bertrand[1,2]

[1]Institute of Pediatric Hematology and Oncology, Hospices Civils de Lyon, Lyon, France
[2]Claude Bernard University – Lyon 1, Lyon, France
[3]Laboratory of Hematology, Lyon Sud Hospital, Hospices Civils de Lyon, Lyon, France
[4]Laboratory of Hematology, Center of Biology and Pathology East, Hospices Civils de Lyon, Lyon, France
[5]Laboratory of Hematology, CHU Lille, Lille, France

Correspondence
Mathilde Penel-Page, MD, Institut d'Hématologie et d'Oncologie Pédiatrique, 1 Place Joseph Renaut, 69008 Lyon, France.
Email: mathilde.penel-page@ihope.fr

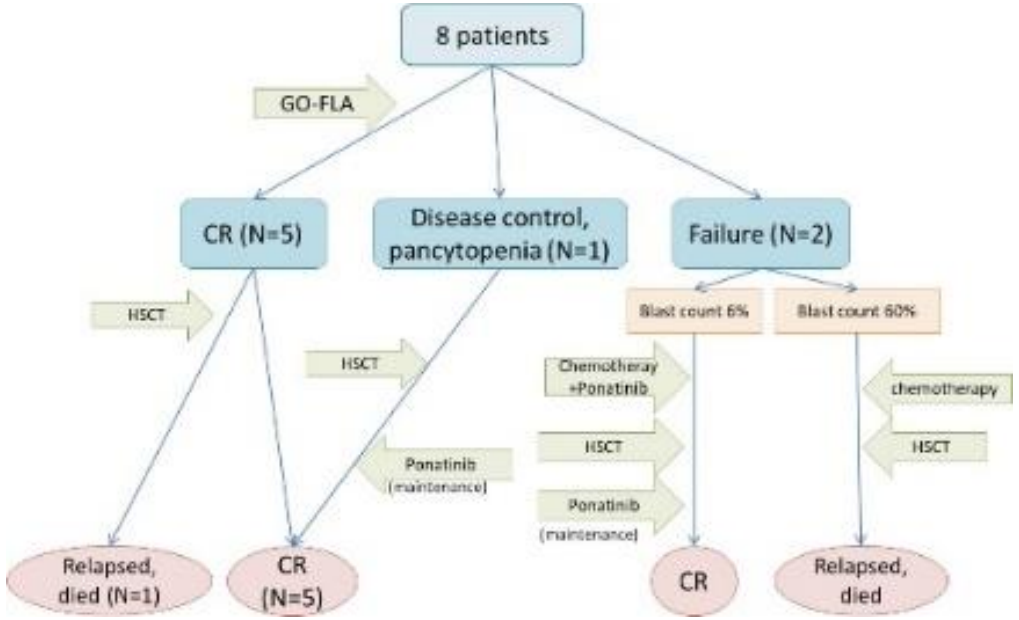
Abstract

Context: Acute myeloid leukemia (AML) is a rare disease in children, with only 50% to 60% event-free survival. Among patients with AML, 10% do not respond to first-line chemotherapy. There is no recommendation concerning second-line treatments. Gemtuzumab ozogamicin (GO) is a monoclonal antibody targeting CD33, linked to calicheamicin. We report the efficacy and tolerance of a salvage regimen of fludarabin, cytarabine, and GO (FLA-GO) in patients refractory to first-line treatment.

Methods: Eight patients (median age 14.5 years), who had more than 2% minimal residual disease (MRD) by flow cytometry (MRD flow), received gemtuzumab 3 mg/m^2 on days 1, 4, 7, associated with cytarabine 2000 mg/m^2 and fludarabin 30 mg/m^2 on days 1 to 5.

Results: Six patients achieved complete remission (CR) (blast count morphology $\leq 5 \times 10^{-2}$, CR-MRD flow $< 1 \times 10^{-3}$ for four patients). Five patients received a second course. We observed 11 episodes of febrile neutropenia, including 6 septicemias without complication. There was no fungal infection or toxic death. Two patients received granulocyte colony stimulating factor. One patient had partial platelet recovery; one, prolonged pancytopenia. All patients received hematopoietic stem cell transplantation (HSCT). We observed five mild-to-severe sinusoidal obstruction syndromes during HSCT procedures, particularly in patients who did not receive defibrotide prophylaxis. At the date of last contact (median follow-up: 58 months; range: 22-78), six patients were in continuous CR with negative MRD. Two patients died of post-HSCT relapse.

Conclusion: FLA-GO is a good salvage regimen for pediatric refractory AML, with significant but acceptable toxicity. HSCT is mandatory to achieve sustained CR in these patients.



Of the eight patients treated, five achieved CR
And in one patient disease was controlled, but MRD < 10^{-2}
Among these 6 patients, one patient died because of AML relapse, and the others achieved CR and complete chimerism, with MRD-flow undetectable

GO in Relapsed or Refractory AML

Gemtuzumab Ozogamicin Improves Event-Free Survival and Reduces Relapse in Pediatric *KMT2A*-Rearranged AML: Results From the Phase III Children's Oncology Group Trial AAML0531

Authors: Jessica A. Pollard, MD, Erin Guest, MD, Todd A. Alonzo, PhD, Robert B. Gerbing, MS, Mike R. Loken, PhD, Lisa Eidenschink Brodersen, PhD, E. Anders Kolb, MD, Richard Aplenc, MD, PhD, Soheil Meshinchi, MD, PhD, Susana C. Raimondi, PhD, Betsy Hirsch, PhD, and Alan S. Gamis, MD
AUTHORS INFO & AFFILIATIONS

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Abstract

Purpose

We investigated the impact of the CD33-targeted agent gemtuzumab ozogamicin (GO) on survival in pediatric patients with *KMT2A*-rearranged (*KMT2A*-r) acute myeloid leukemia (AML) enrolled in the Children's Oncology Group trial AAML0531 (NCT01407757).

Methods

Patients with *KMT2A*-r AML were identified and clinical characteristics described. Five-year overall survival (OS), event-free survival (EFS), disease-free survival (DFS), and relapse risk (RR) were determined overall and for higher-risk versus not high-risk translocation partners. GO's impact on response was determined and outcomes based on consolidation approach (hematopoietic stem cell transplant [HSCT] *v* chemotherapy) described.

Results

Two hundred fifteen (21%) of 1,022 patients enrolled had *KMT2A*-r AML. Five-year EFS and OS from study entry were 38% and 58%, respectively. EFS was superior with GO treatment (EFS 48% with GO *v* 29% without, *P* = .003), although OS was comparable (63% *v* 53%, *P* = .054). For patients with *KMT2A*-r AML who achieved complete remission, GO was associated with lower RR (40% GO *v* 66% patients who did not receive GO [No-GO], *P* = .001) and improved 5-year DFS (GO 57% *v* No-GO 33%, *P* = .002). GO benefit was observed in both higher-risk and not high-risk *KMT2A*-r subsets. For patients who underwent HSCT, prior GO exposure was associated with decreased relapse (5-year RR: 28% GO and HSCT *v* 73% No-GO and HSCT, *P* = .006). In multivariable analysis, GO was independently associated with improved EFS, improved DFS, and reduced RR.

Conclusion

GO added to conventional chemotherapy improved outcomes for *KMT2A*-r AML; consolidation with HSCT may further enhance outcomes. Future clinical trials should study CD33-targeted agents in combination with HSCT for pediatric *KMT2A*-r AML.

study on Pediatric KMT2A-Rearranged AML,
received GO before HSCT
findings:

1. GO exposure before HSCT improves post-HSCT outcomes even without impacting MRD
2. GO does not significantly impact early on MRD clearance in KMT2A-r AML patients
3. Even patients in low CD33 quartiles still showed clinical benefit from GO in this study

GO in Relapsed or Refractory AML
GO as monotherapy

Safety and efficacy of gemtuzumab ozogamicin in pediatric patients with advanced CD33⁺ acute myeloid leukemia

Clinical Trials & Observations

Robert J. Arceci, Jane Sande, Beverly Lange, Kevin Shannon, Janet Franklin, Raymond Hutchinson, Terry A. Vik, David Flowers, Richard Aplenc, Mark S. Berger, Matthew L. Sherman, Franklin O. Smith, Irwin Bernstein, Eric L. Sievers

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Article history

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Abstract

This open-label, dose-escalation study evaluated the safety and efficacy of single-agent gemtuzumab ozogamicin, a humanized anti-CD33 antibody–targeted chemotherapeutic agent, for pediatric patients with multiple relapsed or primary refractory acute myeloid leukemia (AML). Twenty-nine children 1 to 16 years of age (relapsed disease, 19; refractory disease, 10) received gemtuzumab ozogamicin ranging from 6 to 9 mg/m² per dose for 2 doses (separated by 2 weeks) infused over 2 hours. All patients had anticipated myelosuppression. Other toxicities included grade 3/4 hyperbilirubinemia (7%) and elevated hepatic transaminase levels (21%); the incidence of grade 3/4 mucositis (3%) or sepsis (24%) was relatively low. One patient treated at 9 mg/m² developed veno-occlusive disease (VOD) of the liver and defined the dose-limiting toxicity. Thirteen patients underwent hematopoietic stem-cell transplantation less than 3.5 months after the last dose of gemtuzumab ozogamicin; 6 (40%) developed VOD. Eight of 29 (28%) patients achieved overall remission. Remissions were comparable in patients with refractory (30%) and relapsed (26%) disease. Mean multidrug resistance-protein–mediated drug efflux was significantly lower in the leukemic blasts of patients achieving remission ($P < .005$). Gemtuzumab ozogamicin was relatively well tolerated at 6 mg/m² for 2 doses and was equally effective in patients with refractory and relapsed disease. Further studies in combination with standard induction therapy for childhood AML are warranted.

Safety and efficacy of gemtuzumab ozogamicin in pediatric patients with advanced CD33⁺ acute myeloid leukemia

Summary

The prognosis of children with relapsed/refractory acute myeloid leukaemia (AML) is poor, and new therapies are needed. Gemtuzumab ozogamicin (GO) is an anti-CD33 antibody linked to the antitumor antibiotic calicheamicin. We conducted an investigator-initiated phase II study with GO to assess its efficacy and safety, administering two dosages of 7·5 mg/m² with a 14 d-interval. Thirty children who were refractory to re-induction at first relapse or suffered from second relapse of AML received a total of 64 infusions of GO. The response rate [complete remission (CR) and CR with insufficient platelet recovery] was 37%. Nine patients were subsequently transplanted (median time to transplant, 4 weeks, range 3–21 weeks), and three of these patients are currently in continuous CR with a median follow-up of >3 years, and can considered to be cured. This resulted in a statistically significant survival advantage for children who responded to GO *versus* those who did not [27% (standard error 13%) vs. 0%, respectively, P = 0·001]. All other children died, mainly from progressive disease. The treatment was generally well tolerated by most patients. The frequency of transient transaminatis was low. All but one patient received defibrotide prophylaxis during the transplant procedure, and no cases of veno-occlusive disease were noted. This study showed a favourable safety/efficacy profile of single-agent GO in children with refractory first or second relapse of AML.

GO in Relapsed or Refractory AML
GO as monotherapy

- GO as monotherapy for relapsed Pediatric AML had a significantly higher survival rate than children who did not receive the treatment
- GO provided enough disease control to undergo HSCT

Summary

- GO therapy before HSCT, in patients who didn't respond well to traditional chemotherapy, may improve their prognosis by lowering MRD levels before transplantation without raising transplant-related mortality
- GO, besides routine chemotherapy, is a good salvage regimen for pediatric refractory AML, and influences decreasing MRD (from 2% to < $\mathbf{10^{-3}}$)
- GO exposure before HSCT improves post-HSCT outcomes even without impacting MRD in KMT2A-r AML patients

GO After HSCT

Preliminary results of the safety of immunotherapy with gemtuzumab ozogamicin following reduced intensity allogeneic stem cell transplant in children with CD33+ acute myeloid leukemia

Purpose: Myeloablative allogeneic stem cell transplantation (SCT) has been successful in the treatment of childhood acute myeloid leukemia (AML), but may be associated with significant toxicity and recurrent disease. Reduced-intensity allogeneic SCT may offer a less toxic approach to patients with AML. Targeted immunotherapy with gemtuzumab ozogamicin has been shown to be safe, well tolerated in children, and, as a single agent, gemtuzumab ozogamicin has induced responses in 30% of patients with recurrent CD33+ AML. There are no safety data with gemtuzumab ozogamicin post allogeneic SCT in children. Therefore, we explored the feasibility and toxicity of targeted immunotherapy following reduced-intensity allogeneic SCT in children with CD33+ AML.

Experimental design: Eight patients with CD33+ AML received a reduced-intensity allogeneic SCT following fludarabine 30 mg/m2 for 6 days and busulfan 3.2 mg/kg (<4 years, 4 mg/kg/d) for 2 days. Donor sources included six 6/6 HLA-matched related peripheral blood stem cells, one 6/6 sibling cord blood, and one 4/6 unrelated cord blood.

Results: Day 30 and day 60 donor chimerisms in seven of eight evaluable patients were 96 +/- 2% (n = 7) and 94 +/- 3% (n = 6), respectively. Five of six patients (too early for one patient) received two doses of gemtuzumab ozogamicin and one patient received only one dose. After each dose, all patients developed grade 4 neutropenia, with recovery on median days 16 and 13, respectively, after dose 1 and dose 2. Grade 4 thrombocytopenia was only observed in 2 of 11 gemtuzumab ozogamicin courses. No patients have developed dose-limiting toxicity secondary to gemtuzumab ozogamicin.

Conclusions: The administration of gemtuzumab ozogamicin post reduced-intensity allogeneic SCT in children with average risk AML is feasible and well tolerated with minimal toxicity. The maximal tolerated dose has yet to be determined for gemtuzumab ozogamicin post reduced-intensity allogeneic SCT in children with CD33+ AML. Additional studies in a larger group of patients will be required to adequately assess the safety of this approach.

- This study used Gemtuzumab Ozogamicin to reduce-intensity allogeneic SCT
- GO therapy post-HSCT was a part of a planned consolidation strategy, not because of MRD positivity.
- No relapses happened among patients who completed two GO doses.

A Phase I Study of Reduced-Intensity Conditioning and Allogeneic Stem Cell Transplantation Followed by Dose Escalation of Targeted Consolidation Immunotherapy with Gemtuzumab Ozogamicin in Children and Adolescents with CD33$^+$ Acute Myeloid Leukemia

Stacey Zahler [1], Monica Bhatia [2], Angela Ricci [2], Sumith Roy [1], Erin Morris [1], Lauren Harrison [1], Carmella van de Ven [1], Sandra Fabricatore [1], Karen Wolownik [1], Erin Cooney-Qualter [3], Lee Ann Baxter-Lowe [4], Paul Luisi [1], Olga Militano [1], Morris Kletzel [5], Mitchell S. Cairo [1,6,*]

[1] *Department of Pediatrics, New York Medical College, Valhalla, New York*
[2] *Department of Pediatrics, Columbia University, New York, New York*
[3] *Department of Pediatrics, Mount Sinai Medical School, New York, New York*
[4] *Department of Pathology, Children's Hospital of Los Angeles, Los Angeles, California*
[5] *Department of Pediatrics, Northwestern University, Chicago, Illinois*
[6] *Departments of Medicine, Pathology, Microbiology and Immunology, and Cell Biology and Anatomy, New York Medical College, Valhalla, New York*

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A B S T R A C T

Myeloablative conditioning and allogeneic hematopoietic stem cell transplant (alloHSCT) in children with acute myeloid leukemia (AML) in first complete remission (CR1) may be associated with significant acute toxicity and late effects. Reduced-intensity conditioning (RIC) and alloHSCT in children is safe, feasible, and may be associated with less adverse effects. Gemtuzumab ozogamicin (GO) induces a response in 30% of patients with CD33$^+$ relapsed/refractory AML. The dose of GO is significantly lower when combined with chemotherapy. We examined the feasibility and toxicity of RIC alloHSCT followed by GO targeted immunotherapy in children with CD33$^+$ AML in CR1/CR2. Conditioning consisted of fludarabine 30 mg/m^2 × 6 days, busulfan 3.2 to 4 mg/kg × 2 days ± rabbit antithymocyte globulin 2 mg/kg × 4 days followed by alloHSCT from matched related/unrelated donors. GO was administered ≥60 days after alloHSCT in 2 doses (8 weeks apart), following a dose-escalation design (4.5, 6, 7.5, and 9 mg/m^2). Fourteen patients with average risk AML received RIC alloHSCT and post-GO consolidation: median age 13.5 years at transplant (range, 1 to 21), male-to-female 8:6, and disease status at alloHSCT 11 CR1 and 3 CR2. Eleven patients received alloHSCT from 5-6/6 HLA-matched family donors: 8 received peripheral blood stem cells, 2 received bone marrow, and 1 received related cord blood transplantation. Three patients received an unrelated allograft (two 4-5/6 and one 9/10) from unrelated cord blood unit and bone marrow, respectively. Neutrophil and platelet engraftment was observed in all assessable patients (100%), achieved at median 15.5 days (range, 7 to 31) and 21 days (range, 10 to 52), respectively. Three patients received GO at dose level 1 (4.5 mg/m^2 per dose), 5 at dose level 2 (6 mg/m^2 per dose), 3 at dose level 3 (7.5 mg/m^2 per dose), and 3 at dose level 4 (9 mg/m^2 per dose). Three of 14 patients received only 1 dose of GO after alloHSCT. One patient experienced grade III transaminitis, which resolved; no grade IV transaminitis, no grade III/IV hyperbilirubinemia, or sinusoidal obstructive syndrome were observed. The second dose of GO was given at median of 143 days (range, 120 to 209) after alloHSCT. Probability of grades II to IV acute and chronic graft-versus-host disease were 21% and 33.5%, respectively. Probability of overall survival after RIC alloHSCT and GO consolidation at 1 and 5 years was 78% and 61%, respectively. Probability of 5-year event-free survival after RIC alloHSCT and GO consolidation in patients in CR1 was 78%. No dose-limiting toxicities probably or directly related to GO were observed in this cohort. This preliminary data demonstrate that RIC followed by alloHSCT and consolidation with GO appears to be safe in children and adolescents with CD33$^+$ AML in CR1/CR2. A phase II trial is currently underway investigating this approach with a GO dose of 9 mg/m^2 per dose.

GO After HSCT

In a Phase I Study of Reduced-Intensity Conditioning(RIC) and Allogeneic Stem Cell Transplantation Followed by GO in Children and Adolescents, it was shown that GO may reduce relapse risk after HSCT by eradicating residual leukemic cells

Summary

- Gemtuzumab Ozogamicin has been used after HSCT to reduce-intensity allogeneic SCT

- Reduced-Intensity Conditioning(RIC) and Allogeneic Stem Cell transplantation followed by GO may reduce RR after HSCT

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Thank You

Amir Ali Hamidieh M.D.

Professor of Pediatric Hematology/Oncology & Stem Cell Transplant
Director, Pediatric Cell & Gene Therapy Research Center
Tehran University of Medical Sciences
Director, Pediatric Stem Cell Transplant Department
Children's Medical Center
Tehran, Iran

aahamidieh@tums.ac.ir

Phone Number:

+98 912 1593270