From the Young to the Grown-up; Pharmacotherapy Updates in Acute Lymphoblastic Leukemia (ALL)

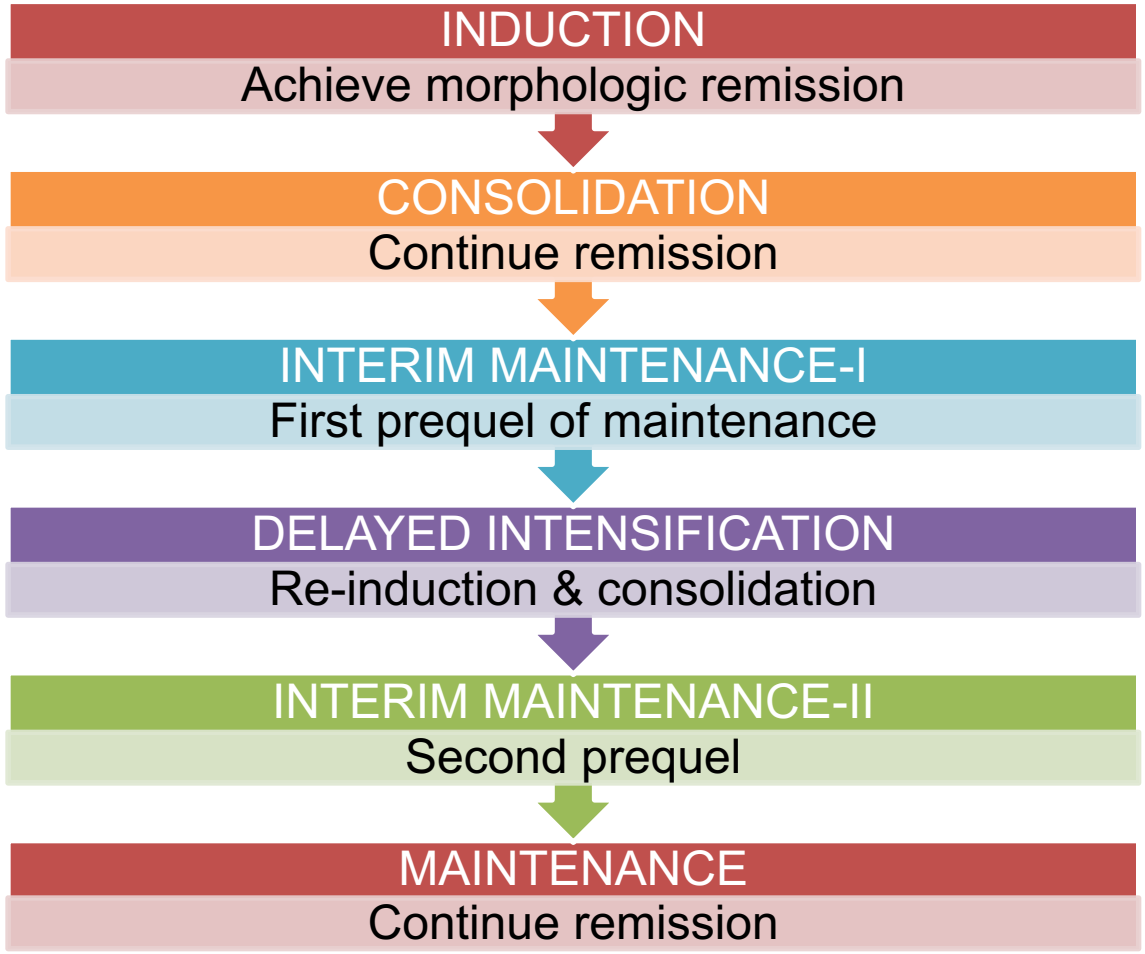
Michelle Bustamante, PharmD, BCPPS
Pediatric Hematology Oncology Pharmacist Specialist
Miami Cancer Institute

Eduardo A. Guizan Corrales, PharmD, BCOP
Hematology Oncology Pharmacist Specialist
Miami Cancer Institute

Oncology Pharmacotherapy Conference
May 20, 2023

Pediatric ALL

Pediatric ALL - Treatment Overview



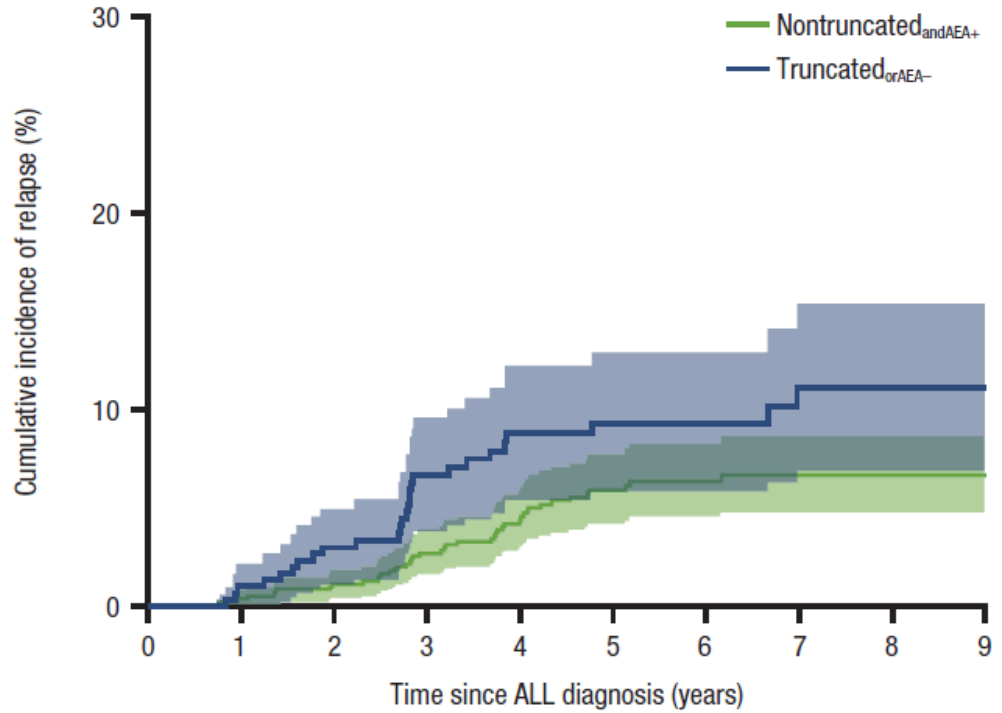
- The most common childhood cancer is acute lymphoblastic leukemia (ALL)
- Children's Oncology Group (COG) Largest organization devoted exclusively to childhood and adolescent cancer research.
  - about 90% of children with the most common form of ALL will survive

www.cancer.net/cancer-types/childhood-cancer/statistics

Importance of Asparaginase

- Asparaginase is the backbone of treatment for pediatric ALL, improving induction response rates and prolonging remission duratior
- Prolonged exposure and intensified doses of asparaginase has been shown benefit in adult ALL patients

Incidence of Relapse



Number at risk									
Nontruncated andAEA+	810	788	700	586	451	333	228	133	46
Truncated orAEA–	292	281	242	199	163	122	92	53	26

Sandley, M., et. al. J. Leuk. Lymphoma (2023)

Asparaginase

LONG ACTING

Pegaspargase

Approved 1994

Use in patients 22 y/o and older.

Dose:2500 units/m^2 (ped); 2000 units/m^2 (adult).

Half life~ 5.8 days (IM); ~5.3 days (IV); up to 7 days for naïve pts.

Asparagine depletion: 2-4 wks (IV); 21 days (IM)

Shelf life: 8 months

Calaspargase pegol-mknl

Approved 2018

Use in patients 1 month to 21 y/o.

Dose : 2500 units/m^2.

Half life: ~16 days.

Asparagine depletion up to 25 days after 1 dose.

Shelf life: 36 months

SHORT ACTING

Asparaginase erwinia chrysanthemi (recombinant)-rywn

Approved 2021

Use in patients with hypersensitivity to long acting asparaginase

Dose: 25 mg/m^2 Q48H (if replacing calaspargase 11 doses/ if replacing pegaspargase 7 doses) **-or-**

25 mg/m^2 M/W & 50 mg/m^2 Fridays (if replacing calaspargase 9 doses/ if replacing pegaspargase 6 doses)

Changes to Treatment

Calaspargase-pegol

- Newly diagnosed patients on or after December 1, 2022
- Age at diagnosis 1 month-21 y/o

Pegaspargase

- Patients who started treatment prior to December 1, 2022
- Age at diagnosis ≥ 22 y/o

Servier Pharmaceuticals (2022)

Changes to Treatment

Children's Oncology Group (COG) Protocols

- AALL1731*, AALL1732, AALL1631 and AALL1621 pegaspargase replaced with calaspargase-pegol
- AALL1821 to be amended
  - Pegaspargase will continue to be given on Days 2 & 16 of reinduction (VXLD)
  - Calaspargase-pegol will be given on Day 2 ONLY (1 dose) of reinduction (VXLD) regimen
- For industry sponsored studies, refer to the sponsor directly for guidance

Adolescent & Young Adult (AYA) (non-COG) Protocols

- For patients 22 years of age and older, patient will start and remain on pegaspargase
- For patients 20-21 y/o, consult with manufacturer for further guidance on which product to order.
  - Up to provider experience and/or preference

*substitution not permitted in induction

Militano, O. et. al. Asparaginase products update (2022)

Clinical Pearls

- The **age** of the patient at diagnosis is important:
  - Calaspargase-pegol approval for: 1 month to 21 y/o
  - Pegaspargase approval for 22 y/o and older
  - If patient “ages out” while on treatment, consult with COG and or manufacturer for further guidance
- Once started on recombinant *Erwinia* (due to hypersensitivity to long acting asparaginase), switching back to a long acting asparaginase product is not recommended
- Levels can also be obtained with recombinant *Erwinia*, timing is important:
  - If 48 hour dosing: obtain level prior to next dose
  - If M/W/F, obtain level prior Friday dose or Monday dose

Adult ALL

Management of Adult ALL

- Frontline: Younger Adults
  - Pediatric regimens is the standard of care
- Frontline: Older Adults
  - Aims to do less aggressive strategies
- Clinical trials including chemotherapy + targeted agents
  - Philadelphia chromosome (Ph) positive B-ALL: Chemotherapy free regimens may be best
- Novel Agents includes **bispecific T-cell engager therapy, CD22 monoclonal antibodies**, chimeric antigen receptor T-cell therapy (CAR T), B-cell lymphoma 2 inhibitors

MCI ALL Pathways

B-ALL

- Ph(-) B-ALL (Up to 40 y/o): CALGB 10403
- Ph(-) B-ALL (>40 y/o): HyperCVAD +/- Rituximab, **Mini-HyperCVD + Inotuzumab Ozogamicin,** Mini-HyperCVD + Venetoclax, Steroids + Vincristine
- Ph(+) B-ALL (Up to age 60 y/o): HyperCVAD + Tyrosine Kinase Inhibitors +/- Rituximab or **Dasatinib + Steroids + Blinatumomab**
- Ph(+) B-ALL (>65 y/o; less fit): **Tyrosine Kinase Inhibitors + Steroids +/- Blinatumomab** (low intensity), EWALL-PH-01 (moderate intensity)

T-ALL

- T-ALL (Up to 50 y/o): AALL0434 +/- Nelarabine, Hyper-CVAD

Salvage Therapy

- Ph-positive B-ALL
  - Clinical trial
  - Tyrosine Kinase Inhibitors + chemotherapy
  - **Blinatumomab**
  - **Inotuzumab Ozogamicin**
  - CAR T (Tisagenlecleucel or Brexucabtagene autoleucel)
- Ph-negative B-ALL
  - Clinical trial
  - **Blinatumomab**
  - **Inotuzumab Ozogamicin + Mini Hyper-CVD +/- Blinatumomab**
  - CAR T (Tisagenlecleucel or Brexucabtagene autoleucel)
- T-ALL
  - Nelarabine +/- etoposide+ cyclophosphamide

Blinatumomab

Mechanism of Action: Bispecific T-cell engager which binds to CD19 expressed on B-cells and CD3 expressed on T-cells		
Drug	Dose	Notes
Blinatumomab	Varies per protocol: Minimal Residual Disease (MRD)+: 28 mcg daily continuous intravenous infusion (CIVI) on days 1-28 of a 6-weeks cycle (Cycles 1-4) Relapsed/Refractory: 9 mcg daily CIVI on days 1-7, followed by 28 mcg daily CIVI on days 8-28 of a 6-weeks cycle (Cycles 1) then 28 mcg daily CIVI on days 1-28 of a 6-weeks (Cycles 2-5) and 12-weeks cycle (Cycles 6-9) D-ALBA: 28 mcg daily CIVI on days 1-28 of a 6-weeks cycle (Cycles 1-5) Mini-HyperCVD: 9 mcg daily CIVI on days 1-4, followed by 28 mcg daily CIVI on days 5-28 (Cycles 1) then 28 mcg daily CIVI on days 1-28 of a 6-weeks (Cycles 2-4) Do **not** flush infusion line	• Hospitalization is recommended for the first and second cycle or if therapy is interrupted for 4 or more hours • Premedicate with dexamethasone one hour prior to the first dose of each cycle, step-up dose, dose interruption (>4 hrs) • Adverse Drug Events (ADE): Cytokine release syndrome, infusion reactions, neurotoxicity, infection, pancreatitis, and tumor lysis syndrome • Monitoring: CBC with diff, LFT/Tbili

Blinatumomab: Literature Review

Dasatinib-Blinatumomab for Ph-Positive Acute Lymphoblastic Leukemia in Adults (D-ALBA) (Foà R, Bassan R, Vitale A, et al. N Engl J Med. 2020;383(17):1613-1623)	
Design	• Phase 2 single-group trial in adults with newly diagnosed Ph-positive ALL where dasatinib plus glucocorticoids were administered followed by two cycles of blinatumomab (N = 63) • The primary end point was a sustained molecular response in the bone marrow after treatment
Results	• A complete remission was observed in 98% of patients. At the end of dasatinib induction therapy (day 85), 29% of the patients had a molecular response, and this percentage increased to 60% after two cycles of blinatumomab. At a median follow-up of 18 months, overall survival was 95% and disease-free survival was 88%
Conclusions	• A chemotherapy-free induction and consolidation first-line treatment with dasatinib and blinatumomab was associated with high incidences of molecular response and survival and few toxic effects of grade 3 or higher in adults with Ph-positive ALL

Ponatinib and blinatumomab for Philadelphia chromosome-positive acute lymphoblastic leukemia (Jabbour E, Short NJ, Jain N, et al. Lancet Haematol. 2023;10(1):e24-e34)	
Design	• Single-center, single-arm, phase 2 study in patients aged 18 years or older with newly diagnosed or relapsed or refractory Ph-positive acute lymphoblastic leukemia or chronic myeloid leukemia in lymphoid blast phase (N = 60) • The primary endpoints were complete molecular response in patients with newly diagnosed disease and overall response in patients with relapsed or refractory disease or chronic myeloid leukemia in lymphoid blast phase
Results	• At the median duration of follow-up of 16 months, 33 (87%) of 38 evaluable patients newly diagnose had a complete molecular response, 12 (92%) of 13 evaluable patients with relapsed or refractory disease had an overall response, and 5 (83%) of 6 patients with chronic myeloid leukemia in lymphoid blast phase had an overall response • One (2%) patient discontinued blinatumomab due to tremor. Three (5%) patients discontinued ponatinib secondary to cerebrovascular ischemia, portal vein thrombosis, and coronary artery stenosis in one patient each
Conclusions	• The chemotherapy-free combination of ponatinib and blinatumomab resulted in high rates of complete molecular response in patients with newly diagnosed and relapsed or refractory Ph-positive acute lymphoblastic leukemia

Blinatumomab: Literature Review

Consolidation Therapy with Blinatumomab Improves Overall Survival in Newly Diagnosed Adult Patients with B-Lineage Acute Lymphoblastic Leukemia in Measurable Residual Disease Negative Remission: Results from the ECOG-ACRIN E1910 Randomized Phase III National Cooperative Clinical Trials Network Trial (Litzow M, Sun Z, Paietta E, et al. Blood (2022) 140 (Supplement 2): LBA-1)	
Design	• A phase 3 trial randomizing patients to conventional chemotherapy with or without blinatumomab to determine if patients who become MRD negative (<0.01%) after induction chemotherapy can have improved outcomes with the addition of blinatumomab (N = 224) • The primary objective of the trial was to compare the overall survival (OS) in MRD negative patients who received blinatumomab in conjunction with chemotherapy to that of patients who received chemotherapy alone
Results	• Among the MRD negative patients, at the third interim efficacy analysis, the upper boundary for efficacy analysis was crossed in favor of blinatumomab with a significant improvement in overall survival (median OS: not reached vs. 71.4 months; Hazard ratio 0.42, 95% CI: 0.24 - 0.75; two-sided p=0.003). Median follow-up was 43 months
Conclusions	• The addition of blinatumomab to consolidation chemotherapy resulted in a significantly better overall survival in patients with newly diagnosed B-lineage ALL who were MRD negative after intensification chemotherapy

Inotuzumab Ozogamicin

Mechanism of Action: CD22-directed monoclonal antibody-drug conjugate composed of a calicheamicin component		
Drug	Dose	Notes
Inotuzumab Ozogamicin	Varies per protocol: Relapsed/Refractory: 0.8 mg/m2 IV on day 1 and 0.5 mg/m2 IV on days 8 and 15 (cycle 1) and 0.5 mg/m2 IV on days 1, 8 and 15 (CR/CRi) or 0.8 mg/m2 IV on day 1 and 0.5 mg/m2 IV on days 8 and 15 (Not CR/CRi) (Cycles 2-6) Mini-HyperCVD: 0.6 mg/m2 IV on day 2 and 0.3 mg/m2 IV on days 8 (Cycle 1) and 0.3 mg/m2 IV on days 2, 8 (Cycles 2-4)	• Prior to the first dose, cytoreduction to a peripheral blast count with a combination is recommended for patients with circulating lymphoblasts • Premedication: corticosteroid, an antipyretic, and antihistamine • ADE: hepatotoxicity, bone marrow suppression, hemorrhage, hypersensitivity, infusion related reactions, QT prolongation, sinusoidal obstruction syndrome (SOS) • Monitoring: CBC, LFTs/Tbili and ALP

Inotuzumab Ozogamicin : Literature Review

Inotuzumab ozogamicin in combination with low-intensity chemotherapy for older patients with Philadelphia chromosome-negative acute lymphoblastic leukaemia (Kantarjian H, Ravandi F, Short NJ, et al. Lancet Oncol. 2018;19(2):240-248)	
Design	• A single-arm, phase 2 study in patients with newly diagnosed Ph-negative acute lymphoblastic leukemia (N = 52) • The primary endpoint was progression-free survival at 2 years
Results	• With a median follow-up of 29 months, 2-year progression-free survival was 59% (95% CI 43-72)
Conclusions	• Inotuzumab ozogamicin plus Mini-HyperCVD chemotherapy is a safe and active first-line therapy option in older patients with newly diagnosed acute lymphoblastic leukemia

Chemoimmunotherapy with inotuzumab ozogamicin combined with Mini-HyperCVD, with or without blinatumomab, is highly effective in patients with Philadelphia chromosome–negative acute lymphoblastic leukemia in first salvage (Jabbour E, Sasaki K, Ravandi F, et al. Cancer. 2018;124(20):4044-4055)	
Design	• A phase 2 study evaluating the efficacy and safety of this combination in acute lymphoblastic leukemia patients in first salvage (N = 48) • The primary endpoints of the analysis were the overall response rate and the overall survival. Secondary endpoints included safety measures, progression-free survival (PFS), the rate of subsequent transplant, and the MRD negativity rate of patients who achieved complete response
Results	• Overall, 44 patients (92%) responded, 35 of them (73%) achieving complete response. The overall MRD negativity rate among responders was 93%. Twenty-four patients (50%) received transplant. Veno-occlusive disease (VOD) of any grade occurred in 5 patients (10%). With a median follow-up of 31 months, the median PFS and OS were 11 and 25 months, respectively
Conclusions	• The combination of inotuzumab and low-intensity Mini-HyperCVD chemotherapy with or without blinatumomab shows encouraging results in patients with acute lymphoblastic leukemia in first salvage

Investigational Trials

Trial	Chemo-immunotherapy	Indication	Phase	N	Age (years)	Outcome
MDACC NCT01371630	Induction/consolidation: MiniCVD, CYC/VCN/DEX alternating with MTX/AraC, INO +/- blinatumomab Maintenance: POMP CNS prophylaxis: MTX and AraC	Newly diagnosed Ph-negative B-ALL	II	70	≥60	50% 4-year OS
SWOG 1318 NCT02143414	Induction: Blinatumomab Consolidation: Blinatumomab Maintenance: POMP CNS prophylaxis: MTX	Newly diagnosed Ph-negative B-ALL	II	29	≥65	37% 3-year OS
GMALL-INITIAL1 NCT03460522	Induction: INO/DEX Consolidation: ID-MTX/PEG/ID-AraC, IDA/AraC/CYC/DEX/RTX Maintenance: 6MP/MTX CNS prophylaxis: MTX/DEX/AraC	Newly diagnosed Ph-negative B-ALL	II	45	≥55	91% 1-year OS
EWALL-INO NCT03249870	Pre-phase: Dex 10 mg, Induction1: INO/VCR/DEX Induction2: INO/DEX/CY Consolidation: AraC/DEX, MTX/VCR/6-MP, CY/VP16/MTX Maintenance: POMP CNS prophylaxis: MTX/DEX/AraC	Newly diagnosed Ph-negative B-ALL	II	115	≥55	78.5% 1 year OS
Alliance 041703 NCT03739814	Induction: Inotuzumab Consolidation: blinatumomab CNS prophylaxis: MTX	Newly Diagnosed, Recurrent/Refractory Ph-negative B-ALL	II	29	≥60	Outcome data expected in 2023

Short NJ et al. Blood (2019) 134 (Supplement_1): 823; Advani AS et al. J Clin Oncol. 2022 May 10;40(14):1574-1582; Stelljes M et al. Blood. 2021;138(Supplement 1):2300; Chevallier P et al. Blood 2021;138(Supplement 1):511; O'Dwyer KM. The Hematologist (2022) 19 (3)

Summary

Emerging data showing survival benefits of blinatumomab in minimal residual disease positive and minimal residual disease negative patients

Low intensity treatments with minimal or no traditional chemotherapy is becoming standard of care in adult ALL

Changing role of allogeneic hematopoietic stem cell transplant

From the Young to the Grown-up; Pharmacotherapy Updates in Acute Lymphoblastic Leukemia (ALL)

Michelle Bustamante, PharmD, BCPPS
Pediatric Hematology Oncology Pharmacist Specialist
Miami Cancer Institute

Eduardo A. Guizan Corrales, PharmD, BCOP
Hematology Oncology Pharmacist Specialist
Miami Cancer Institute

Oncology Pharmacotherapy Conference
May 20, 2023