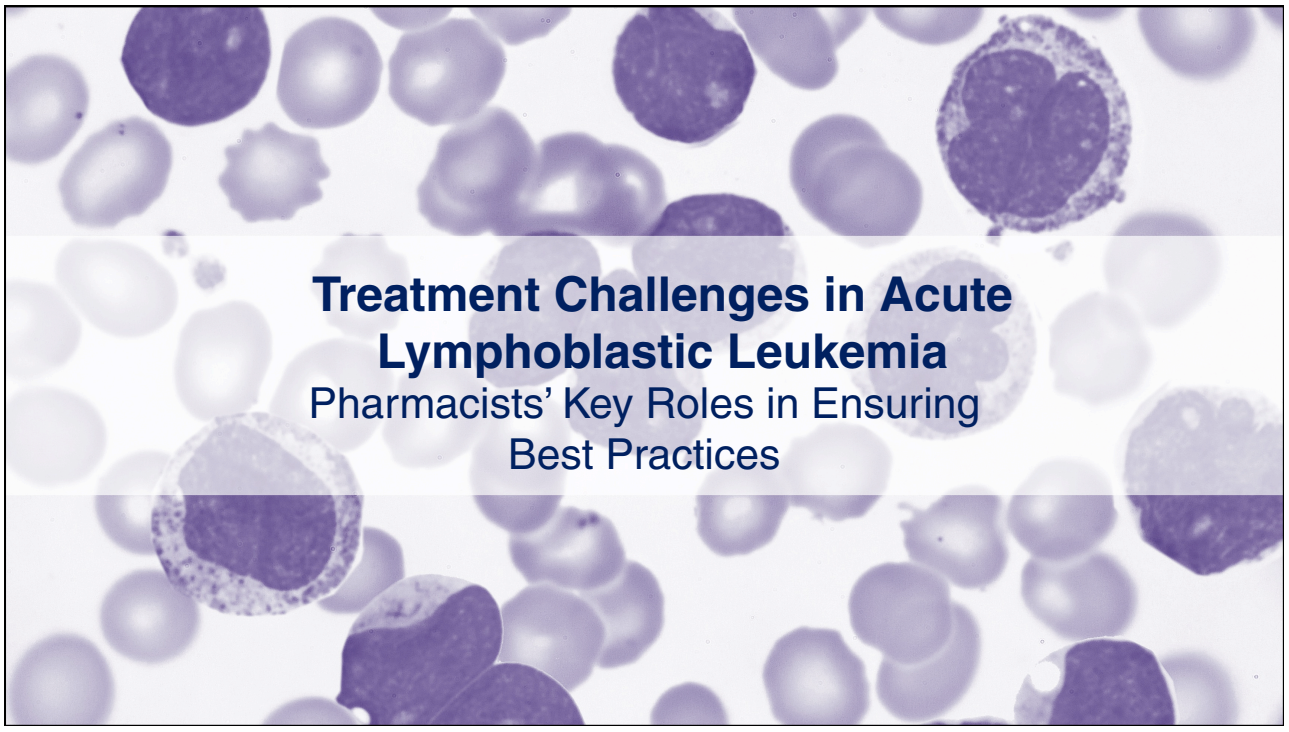

Treatment Challenges in Acute Lymphoblastic Leukemia

Pharmacists' Key Roles in Ensuring Best Practices

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Disclosures

Dr. Fausel has no relevant affiliations or financial relationships with a commercial interest to disclose.

The clinical reviewer, Megan May, PharmD, BCOP, has no actual or potential conflict of interest in relation to this program.

Susanne Batesko, RN, BSN, Robin Soboti, RPh, and Susan R. Grady, MSN, RN-BC, as well as the planners, managers, and other individuals, not previously disclosed, who are in a position to control the content of Postgraduate Healthcare Education (PHE) continuing education activities hereby state that they have no relevant conflicts of interest and no financial relationships or relationships to products or devices during the past 12 months to disclose in relation to this activity. PHE is committed to providing participants with a quality learning experience and to improve clinical outcomes without promoting the financial interests of a proprietary business.

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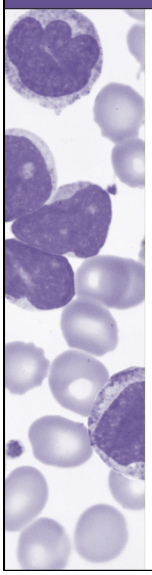
UAN: 0430-0000-18-022-L01-P
Credits: 1.0 hour (0.10 CEU)
Type of Activity: Application

Learning Objectives

- Summarize the current landscape for an overall treatment strategy for adult patients with acute lymphoblastic leukemia (ALL)
- Appraise the role of new and emerging therapies and regimens used to treat adult patients with relapsed/refractory ALL
- Formulate approaches to match adult patients and treatment options for relapsed/refractory ALL on the basis of individual risk factors and prognostic criteria
- Demonstrate pharmacist-driven interventions to reduce the risks and improve the management of adverse events and drug-drug interactions in patients receiving newly approved therapies

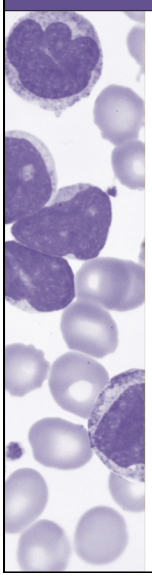
ARS Question #1



Which of the following best characterizes the general treatment strategy for patients with ALL?

A. A single cycle of multi-agent chemotherapy
B. Induction chemotherapy followed by allogeneic stem cell transplant for every patient
C. Induction chemotherapy followed by intensification and then maintenance therapy
D. Induction chemotherapy followed by maintenance therapy

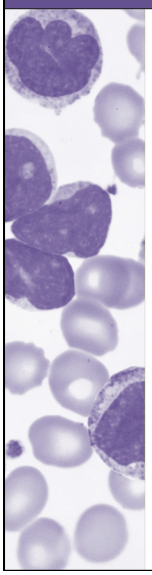
ARS Question #2



Which of the following represents the most appropriate use of liposomal vincristine sulfate injection?

A. Combination therapy with cyclophosphamide, doxorubicin, and prednisone for non-Hodgkin lymphoma
B. Use as an alternative to conventional vincristine formulation for grade 3 or worse neurotoxicity
C. Use in induction therapy for ALL with corticosteroids and L-asparaginase
D. Use as a salvage therapy for relapsed ALL patients with 2 or more prior antileukemic therapies

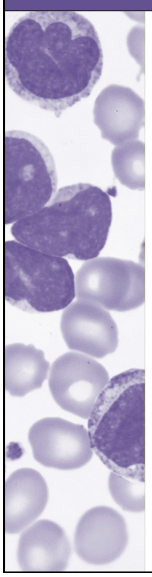
ARS Question #3



Which of the following ALL patient groups has been shown to benefit from chimeric antigen receptor T-cell therapy with tisagenlecleucel?

A. Patients with T-cell ALL
B. Patients with ALL who are older than 50 years of age
C. Patients of any age who are newly diagnosed with ALL
D. Patients aged 25 years or younger with B-cell ALL that has relapsed following conventional treatment

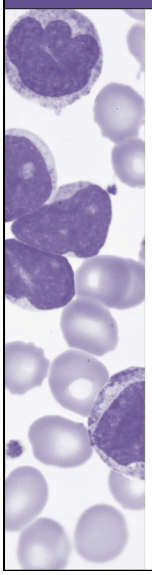
ARS Question #4



How could pharmacists be most beneficial to the care of patients being treated with inotuzumab ozogamicin?

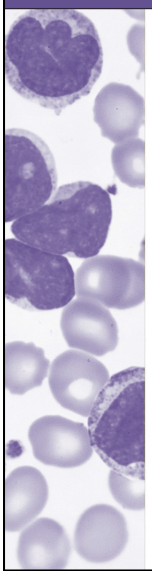
A. Obtain prior authorization for treatment
B. Monitor at bedside for infusion-related toxicity during administration
C. Perform surveillance for changes in hepatic function and avoid use of concomitant hepatotoxic drugs
D. Assess appropriateness for hematopoietic stem cell transplant on the basis of donor availability

ALL Overview



- Clonal expansion of undifferentiated lymphoid precursors resulting in impaired hematopoiesis
- Resultant clinical sequelae is a result of bone marrow failure
- Standard approach to treatment has included multiple rounds of combination chemotherapy with a high index of toxicity and a low chance for outright cure
- Autologous and allogeneic hematopoietic stem cell transplants (HSCT) have been employed with varying degrees of success

ALL Epidemiology



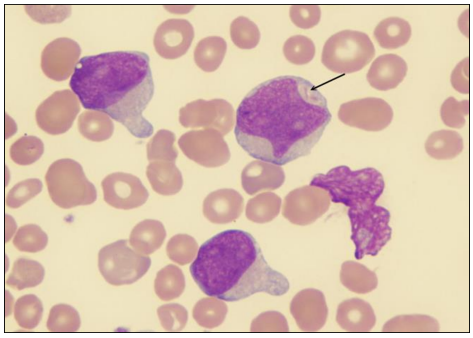
- Estimated 5960 cases in 2018
- Estimated 1470 deaths each year
  - Most deaths are in adults
- 5-year survival (2008-2014): 68.1%*
- Age is a risk factor for ALL
  - Risk is highest in children younger than 5 years old, declines until mid-20's, and begins to rise again after age 50

*Includes pediatric cases

https://seer.cancer.gov/statfacts/html/alyl.html. Accessed June 1, 2018.
https://www.cancer.org/cancer/acute-lymphocytic-leukemia/about/key-statistics.html. Accessed June 1, 2018.

Diagnostic Criteria

At least 20% of cells in peripheral blood or bone marrow are blasts that are lymphoid in origin



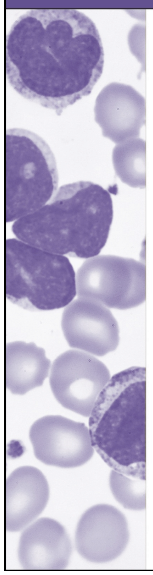
University of Virginia Health System [website]. http://www.healthsystem.virginia.edu/. Accessed May 30, 2018.

Cytogenetics

Risk category	Cytogenetics
Good risk	Hyperdiploidy (51-65 chromosomes; cases with trisomy of chromosomes 4, 10, and 17) t(12;21)(p13;q22): ETV6-RUNX1
Poor risk	Hypodiploidy (< 44 chromosomes) KMT2A rearranged (t(4;11) or others BCR-ABL1 Complex karyotype (5 or more chromosomal abnormalities) Philadelphia chromosome (Ph)-like ALL Intrachromosomal amplification of chromosome 21 (iAMP21)

Moorman AV, et al. *Blood*. 2007;109(8):3189-97.

ALL Overall Treatment Strategy



With CNS prophylaxis
- Induction chemotherapy (1 month)
- Goal: achieve remission

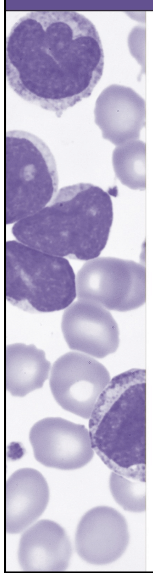
With CNS prophylaxis
- Intensification chemotherapy (4 to 6 months)
- Goal: suppress drug-resistant leukemic clones

PO-based treatment
- Maintenance chemotherapy (18 to 24 months)
- Goal: prevent late relapse

CNS, central nervous system; PO, oral.

Larsen RA, et al. *Blood*. 1998;92(5):1556-64.; Linker C, et al. *J Clin Oncol*. 2002;20(10):2464-71.; Kantarjian H, et al. *J Clin Oncol*. 2000;18(3):547-61.

Standard of Care Drug Therapy



Induction (90% remission rate) plus CNS prophylaxis

Vincristine/corticosteroids	L-asparaginase
Cyclophosphamide	Anthracycline

Intensification plus CNS prophylaxis

Methotrexate/cytarabine (high-dose)	Etoposide
Vincristine/corticosteroids	L-asparaginase

Maintenance

Methotrexate (PO)	6-thioguanine
Vincristine/corticosteroids (intermittent)	6-mercaptopurine

Larsen RA, et al. *Blood*. 1998;92(5):1556-64.; Linker C, et al. *J Clin Oncol*. 2002;20(10):2464-71.; Kantarjian H, et al. *J Clin Oncol*. 2000;18(3):547-61.

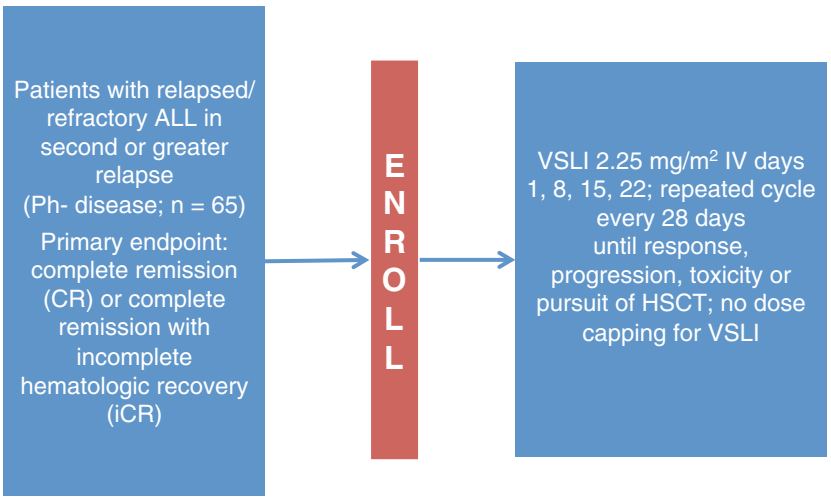
Vincristine Sulfate Liposome Injection (VSLI)

FDA approval	August 2012
FDA-labeled indication	Treatment of adult patients with Ph- ALL in second or greater relapse or whose disease has progressed following 2 or more antileukemic therapies. *This indication is based on overall response rate; clinical benefit such as improvement in overall survival has not been verified.*
Pharmacology	Sphingomyelin/cholesterol liposome-encapsulated formulation of vincristine sulfate. Non-liposomal vincristine sulfate binds to tubulin, altering the tubulin polymerization equilibrium, resulting in altered microtubule structure and function. Non-liposomal vincristine sulfate stabilizes the spindle apparatus, preventing chromosome segregation, triggering metaphase arrest and inhibition of mitosis.
Dosing	2.25 mg/m^2 IV over 1 hour once every 7 days

IV, intravenously.

Marqibo [prescribing information]; 2016.

VSLI for Relapsed/Refractory ALL – Phase II



O'Brien S, et al. *J Clin Oncol.* 2013;31(6):676-83.

Efficacy Results

Parameter	Response (n = 65)	
CR	20%	95% CI, 11.1 – 31.8
CRi	11%	95% CI, 4.4 – 20.9
Partial response (PR)	9%	95% CI, 3.5 – 19
Overall response rate (ORR)	35%	95% CI, 23.8 – 48.3
Time to CR and CRi	median, 54 days	range, 25 – 81
CR and CRi duration	median, 23 weeks	range, 5 – 66
Overall survival (OS)	median, 4.6 months	range, < 1 – > 25
Post-VSLI HSCT	19%	

O'Brien S, et al. *J Clin Oncol.* 2013;31(6):676-83.

Toxicity Results (≥ Grade 3)

Event	n = 65
Neutropenia	16%
Peripheral neuropathy	15%
Thrombocytopenia	7%
Anemia	5%
Tumor lysis syndrome	5%
Abdominal pain	3%
Constipation	3%
Febrile neutropenia	3%
Asthenia	3%
Fatigue	3%

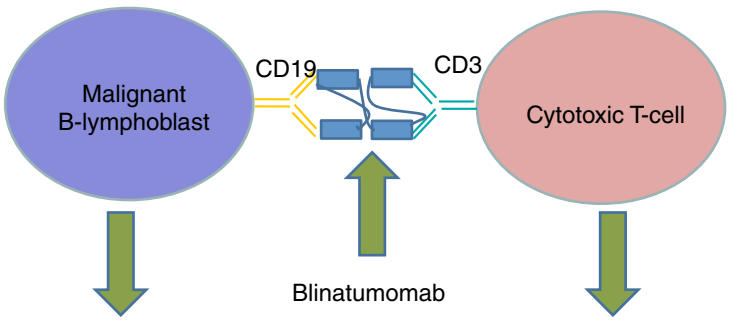
O'Brien S, et al. *J Clin Oncol.* 2013;31(6):676-83.

Blinatumomab

FDA approval	December 3, 2014
FDA-labeled indications	B-cell precursor ALL in first or second remission with minimal residual disease (MRD) greater than or equal to 0.1% Relapsed or refractory B-cell precursor ALL
Pharmacology	Bispecific CD19-directed CD3 T-cell engager that binds to CD19 expressed on the surface of cells of B-lineage origin and CD3 expressed on the surface of T-cells. It activates endogenous T-cells by connecting CD3 in the T-cell receptor complex with CD19 on benign and malignant B cells. This results in the formation of a synapse between the T-cell and the tumor cell, upregulation of cell adhesion molecules, production of cytolytic proteins, release of inflammatory cytokines, and proliferation of T-cells resulting in redirected lysis of CD19+ cells.

Blincyto [prescribing information]; 2018.

Bispecific T-cell Engager (BiTE) Pharmacology



B-cell apoptosis:
- Activation of caspases
- Cleavage of PARP
- Fragmentation of DNA
- Morphologic changes

T-cell proliferation:
- ↑ CD69, CD25
- ↑ Granzymes, perforin
- ↑ Adhesion, cytokines
- ↑ Cell cycle

PARP, poly (ADP-ribose) polymerase.

Nagorsen D, et al. *Pharmacol Ther.* 2012;136(3):334-42.

Blinatumomab Dosing

MRD-positive B-cell ALL	Relapsed/refractory ALL
Induction Cycle 1: Days 1-28: 28 mcg/day* IV Days 29-42: 14 days treatment free	Induction Cycle 1: Days 1-7: 9 mcg/day IV *(for patients who weigh less than 45 kg: 5 mcg/m^2/day dose)* Days 8-28: 28 mcg/day* IV Days 29-42: 14 days treatment free Induction Cycle 2: Days 1-28: 28 mcg/day* IV Days 29-42: 14 days treatment free
Consolidation Cycles 2 through 4: Days 1-28: 28 mcg/day* IV Days 29-42: 14 days treatment free	Consolidation Cycles 3 through 5: Days 1-28: 28 mcg/day* IV Days 29-42: 14 days treatment free Consolidation Cycles 6 through 9: Days 1-28: 28 mcg/day* IV Days 29-84: 56 days treatment free

**For patients who weigh less than 45 kg: 15 mcg/m^2/day dose*

Blincyto [prescribing information]; 2018.

Blinatumomab – Phase III (TOWER)

Patients with relapsed/refractory ALL (Ph-) randomized 2:1 to blinatumomab or standard chemotherapy (n = 405)

Primary endpoint: OS

Median follow-up duration:

11.7 months

RANDOMIZE

Blinatumomab induction cycle:
Days 1-7: 9 mcg/day
Days 8-28: 28 mcg/day*
Days 29-42: 14 days treatment free
Maintenance treatment given as 4-week continuous infusion every 12 weeks

Standard chemotherapy:
FLAG
High-dose cytarabine
High-dose methotrexate
Clofarabine-based regimens

HSCT per investigator discretion

FLAG: fludarabine, cytarabine, and granulocyte colony stimulating factor.

Kantarjian H, et al. *N Engl J Med.* 2017;376(9):836-47.

Efficacy Results

Parameter	Blinatumomab (n = 271)	Chemotherapy (n = 134)	P-value
OS	7.7 months	4 months	P = 0.01
6-month OS	54%	39%	
CR	34%	16%	P < 0.001
Response rate (RR)	44%	25%	P < 0.001
Median duration of remission	7.3 months	4.6 months	
6-month event-free survival (EFS)	31%	12%	
Underwent allogeneic HSCT	24%	24%	

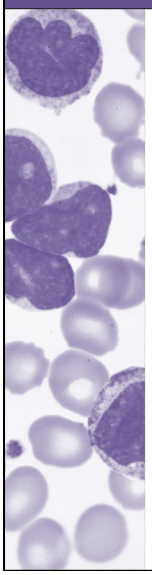
Kantarjian H, et al. *N Engl J Med.* 2017;376(9):836-47.

Toxicity Results (≥ Grade 3)

Event	Blinatumomab (n = 267)	Standard chemotherapy (n = 109)
Premature discontinuation of treatment	12%	8%
Fatal adverse event	19%	17%
Neutropenia	38%	58%
Infection	34%	52%
Elevated liver enzymes	13%	15%
Neurologic events	9%	8%
Cytokine release syndrome (CRS)	5%	0%
Infusion reaction	3%	1%
Lymphopenia	2%	4%
Any platelet decrease	6%	12%
Any white blood cell (WBC) decrease	5%	6%

Kantarjian H, et al. *N Engl J Med.* 2017;376(9):836-47.

Blinatumomab for MRD ALL – Phase II



Patients with precursor B-cell ALL in first or later hematologic CR with persistent or recurrent MRD ($\geq 10^{-3}$) after a minimum of 3 rounds of chemotherapy (n = 116)

Primary endpoint: complete MRD response after Cycle 1

→

Blinatumomab: 15 mcg/m^2/day continuous infusion given over 4 weeks followed by a 2-week treatment-free interval; up to 4 cycles

CNS prophylaxis given before Cycle 1 and after Cycles 2 and 4

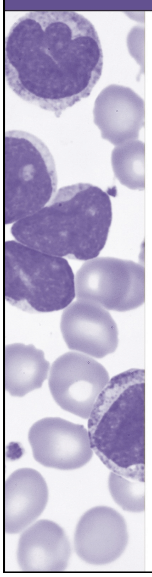
Median follow-up: 29.9 months

→

HSCT per investigator discretion anytime following Cycle 1

Gokbuget N, et al. *Blood*. 2018;131(14):1522-31.

Efficacy Results



Parameter	n = 113
MRD response - overall	88%
MRD response - complete	80%
Relapse-free survival (RFS) at 18 months (Ph-)	54%
Median RFS	18.9 months
Median duration of hematologic remission	Not reached
Median OS	36.5 months
Underwent HSCT in remission	67%

Gokbuget N, et al. *Blood*. 2018;131(14):1522-31.

Toxicity Results (≥ Grade 3)

Event	n = 116
Neutropenia	16%
Any neurologic event	13%
Pyrexia	8%
Leukopenia	6%
ALT increased	5%
Encephalopathy	5%
Thrombocytopenia	5%
Tremor	5%
Anemia	4%
AST increased	4%
Headache	3%

ALT, alanine aminotransferase;
AST, aspartate aminotransferase.

Gokbuget N, et al. *Blood*. 2018;131(14):1522-31.

Inotuzumab Ozogamicin

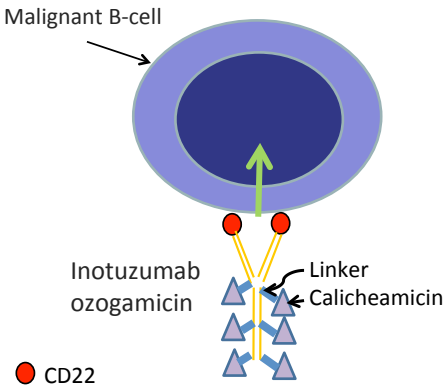
FDA approval	August 17, 2017
FDA-labeled indication	Treatment of adults with relapsed or refractory B-cell precursor ALL
Pharmacology	CD22-directed antibody-drug conjugate (ADC): calicheamicin is covalently bound to the antibody via a linker. The ADC binds to CD22 on B-cells and the ADC-CD22 complex is internalized in the B-cell. Calicheamicin is released from the linker and induces intracellular DNA strand breaks within the B-cell.
Dosing	<u>Cycle 1 (length, 21 days):</u> Day 1: 0.8 mg/m^2 IV Days 8, 15: 0.5 mg/m^2 IV <u>Subsequent cycles (length, 28 days):</u> *If CR:* 0.5 mg/m^2 IV on days 1, 8, 15 *If no CR:* Day 1: 0.8 mg/m^2 IV Days 8, 15: 0.5 mg/m^2 IV

Besponsa [prescribing information]; 2017.

ADC Pharmacology

Inotuzumab ozogamicin

- Binds to CD22
  - –Expressed on B-cells
- ADC-antigen complex internalized by receptor-mediated endocytosis
- Calicheamicin releases from CD22 MoAb intracellularly and induces DNA double-strand breaks resulting in cell death



MoAb, monoclonal antibody.

Herrera AF, Molina A. *Clin Lymph Myeloma Leuk.* 2018;18(7):452-68.e4.

Inotuzumab Ozogamicin – Phase III

Patients with relapsed/refractory ALL (CD22+/ includes Ph+) receiving first or second salvage therapy

(n = 326; data analyzed following 218 patients randomized)

Primary endpoints:

OS and CR

RANDOMIZE

First induction:
Inotuzumab ozogamicin 0.8 mg/m^2 on day 1, then 0.5 mg/m^2 IV on days 8, 15; repeat cycle every 21 days

Consolidation:
Inotuzumab ozogamicin 0.5 mg/m^2 IV on days 1, 8, 15; repeat cycle every 28 days

Standard ALL salvage chemotherapy:
FLAG
Mitoxantrone and cytarabine
High-dose cytarabine

Kantarjian H, et al. *N Engl J Med.* 2016;375(8):740-53.

Efficacy Results

Parameter	Inotuzumab ozogamicin (n = 109)	Salvage chemotherapy (n = 109)	P-value
CR/CRi	81%	29%	< 0.001
CR	36%	17%	0.002
Median OS*	7.7 months	6.7 months	0.04
Median duration of remission	4.6 months	3.1 months	0.03
Subsequent HSCT	41%	19%	P < 0.001
Median PFS	5 months	1.8 months	P< 0.001

*Based on intent-to-treat analysis with 164 patient in inotuzumab ozogamicin arm and 162 patients in the standard chemotherapy arm.

Kantarjian H, et al. *N Engl J Med.* 2016;375(8):740-53.

Toxicity Results (≥ Grade 3)

Parameter	Inotuzumab ozogamicin (n = 139)	Salvage chemotherapy (n = 120)
Febrile neutropenia	11%	18%
Veno-occlusive disease	9%	1%
Sepsis	2%	5%
Pyrexia	1%	1%
Disease progression	4%	2%
Pneumonia	4%	2%
Neutropenic sepsis	2%	2%
Respiratory failure	1%	3%
Abdominal pain	1%	1%
Septic shock	1%	1%
Multi-organ failure	1%	2%

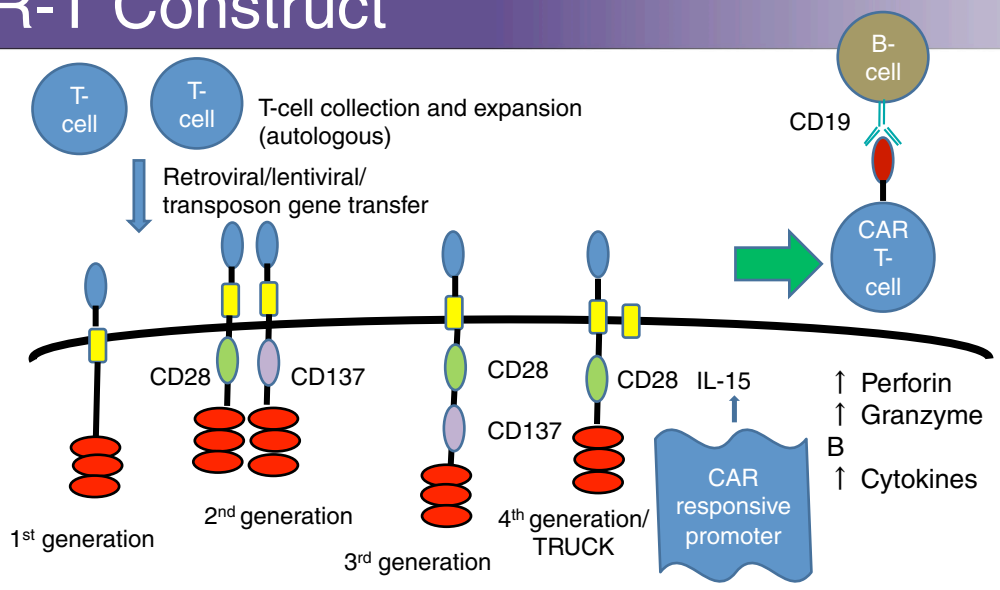
Kantarjian H, et al. *N Engl J Med.* 2016;375(8):740-53.

Tisagenlecleucel

FDA approval	August 30, 2017
FDA-labeled indication	Patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse
Pharmacology	CD19-directed genetically modified autologous T-cell immunotherapy involving reprogramming a patient's own T-cells with a transgene encoding a chimeric antigen receptor (CAR) to identify and eliminate CD19-expressing malignant and normal cells
Dosing	*For patients who weigh more than 50 kg*: 0.1-2.5x10^8 total CAR-positive viable T-cells IV (non-weight based) *For patients who weigh 50 kg or less:* 0.2-5x10^6 CAR-positive viable T-cells per kg of body weight IV

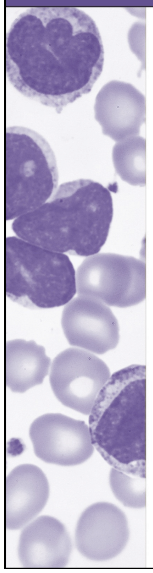
Kymriah [prescribing information]; 2018.

CAR-T Construct



Brown PA, Shaw B. *J Natl Compr Canc Netw.* 2018;16(5s):651-5.

CAR-T Methodology



T-cell collection from the patient

- Leukapheresis
- Ship cells to manufacturer

↓

Clinical cell manufacturing facility

- Engineer T-cells with virus encoding CAR
- Expand CAR-t cell population and harvest

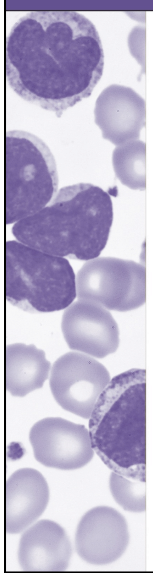
↓

Deliver back to facility for infusion to the patient

- Handled by stem cell lab
- Infuse cells inpatient or outpatient with trained staff

Tran E, et al. *N Engl J Med.* 2017;377(26):2593-6.

Tisagenlecleucel for ALL – Phase II



Pediatric and young adult (≤ 21 years) patients with CD19+ relapsed/refractory B-cell ALL
(n = 75)

Primary endpoint:
overall RR (CR + CRi) within 3 months

Minimum follow-up:
3 months

→

Tisagenlecleucel:
Generated ex vivo with use of autologous T-cells transduced with lentiviral vector to express a CAR containing a CD3-zeta domain to provide T-cell activation signal and a 4-1BB (CD137) domain to provide a costimulatory signal

Lymphodepleting chemotherapy:
Fludarabine/cyclophosphamide or cytarabine/etoposide

→

HSCT per investigator discretion

Maude SL, et al. *N Engl J Med.* 2018;378(5):439-48.

Efficacy Results

Parameter	n = 75
Overall RR	81%
CR	60%
CRi	21%
Median response duration	Not reached
RFS at 6 months	80%
RFS at 12 months	59%
EFS at 6 months	73%
EFS at 12 months	50%
Underwent allogeneic HSCT*	11%
OS at 6 months	90%
OS at 12 months	76%

*All 8 allogeneic HSCT recipients alive at time of last follow-up.

Maude SL, et al. *N Engl J Med.* 2018;378(5):439-48.

Toxicity Results (≥ Grade 3)

Event	≤ 8 weeks after infusion	≥ 8 weeks after infusion
CRS	46%	0%
Hypotension	17%	0%
Lymphocyte decrease	12%	1%
Hypoxia	11%	0%
Bilirubin increase	11%	0%
AST increase	10%	0%
Pyrexia	10%	0%
Decreased neutrophils	9%	2%
Decreased WBC	9%	0%
Decrease in platelets	9%	0%
Decrease in appetite	9%	0%
Acute kidney injury	8%	0%

Maude SL, et al. *N Engl J Med.* 2018;378(5):439-48.

Treatment of CRS

CRS severity	Treatment
Low-grade fever, fatigue, anorexia	Observe in person; exclude infection; administer antibiotics per local guidelines if neutropenic; provide symptomatic support
CRS requiring mild intervention (1 or more of the following): • High fever • Hypoxia • Mild hypotension	Administer antipyretics, oxygen, intravenous fluids and/or low-dose vasopressors as needed

Kymriah [prescribing information]; 2018.

Treatment of CRS

CRS severity	Management
CRS requiring moderate to aggressive intervention (1 or more of the following): • Hemodynamic instability despite intravenous fluids and vasopressor support • Worsening respiratory distress, including pulmonary infiltrates increasing oxygen requirement including high-flow oxygen or mechanical ventilation • Rapid clinical deterioration	• Administer high-dose or multiple vasopressors, oxygen mechanical ventilation, and/or other supportive care as needed • Administer tocilizumab • Repeat tocilizumab as needed at a minimum interval of 8 hours if there is no clinical improvement • If no response to second dose of tocilizumab, consider a third dose of tocilizumab or pursue alternative measures for treatment of CRS • Limit to a maximum of 4 tocilizumab doses • If no clinical improvement within 12 to 18 hours of the first tocilizumab dose, or worsening any time, then administer methylprednisolone 2 mg/kg initially then daily until vasopressors and oxygen are no longer needed then taper

Kymriah [prescribing information]; 2018.

Monitoring Parameters

Agent	Drug toxicity
VSLI	Medication safety – intrathecal injection/drug name Neuropathy/constipation/SIADH Hepatotoxicity Extravasation risk Tumor lysis syndrome
Blinatumomab	CRS Neurotoxicity Tumor lysis syndrome Pancreatitis Leukoencephalopathy Infusion-related reactions

SIADH, syndrome of inappropriate antidiuretic hormone secretion.

Blincyto [prescribing information]; 2018.;
Marqibo [prescribing information]; 2016.

Monitoring Parameters

Agent	Drug toxicity
Inotuzumab ozogamicin	• Infusion-related reactions • Hepatotoxicity including increased veno-occlussive disease/sinusoidal obstruction syndrome with HSCT • Cytoreduction to lower peripheral blast count to < 10,000 mm^3 • Hemorrhage
Tisagenlecleucel	• CRS (administer tocilizumab 8 mg/kg [max dose 800 mg]) • Neurotoxicity • Toxicities of lymphodepleting chemotherapy (e.g., cyclophosphamide/fludarabine) • Hypogammaglobinemia • Prolonged cytopenias (> day +28)

Besponsa [prescribing information]; 2017.;
Kymriah [prescribing information]; 2018.

Drug-Drug Interactions

Agent	Interactions
VSLI	CYP 3A4/5 – inhibitors and inducers P-glycoprotein inhibitors
Blinatumomab	Transient release of cytokines that could suppress CYP isoenzymes (particularly during first 9 days of Cycle 1)
Inotuzumab ozogamicin	QT interval prolongation
Tisagenlecleucel	HIV and the lentivirus used to transduce the patient's cells have may limited, short spans of identical RNA; commercial HIV nucleic acid tests may yield false positive results

CYP, cytochrome P450.

Blincyto [prescribing information]; 2018.; Marqibo [prescribing information]; 2016.; Besponsa [prescribing information]; 2017.; Kymriah [prescribing information]; 2018.

Pharmacy Preparation Issues

Drug	Preparation procedures
VSLI	Requires vincristine/sodium phosphate/sphingomyelin cholesterol liposome to be heated in a water bath (Prep time: 60 to 90 minutes)
Blinatumomab	Continuous infusion: may be prepared for 24-hour, 48-hour, or 7-day bags Solution stabilizer added to NS diluent IV lines primed with diluted drug in NS diluent
Inotuzumab ozogamicin	4-hour expiration following dilution of reconstituted solution (1-hour infusion)
Tisagenlecleucel	Cells are shipped from manufacturer lab to institutional stem cell lab

NS, normal saline.

Blincyto [prescribing information]; 2018.; Marqibo [prescribing information]; 2016.; Besponsa [prescribing information]; 2017.; Kymriah [prescribing information]; 2018.

Drug Costs

Drug	Cost
VSLI	$14,719 per 2.25-mg/m^2 dose*
Blinatumomab	$3,464.60 per 28-mcg dose
Inotuzumab ozogamicin	$44,879 per 0.8-mg/m^2 dose*
Tisagenlecleucel	$475,000 (minus pheresis charge and drug provided by company for free if no clinical response by day 28)

*Doses based on 2.0 m^2 body surface area.

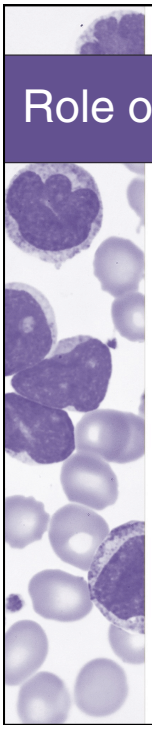
Indiana University Health Department of Pharmacy. Accessed May 30, 2018.

Future Directions

Molecule	Target
Calasparaginase pegol (Cal-PEG)	L-asparagine
Denintuzumab mafodotin	CD19
Eprazutumab +/- Y(90)	CD22
JCAR015	CD19
Ofatumumab	CD20
Bosutinib, nilotinib, dasatinib	Ph+ ALL

Angiolillo AL, et al. *J Clin Oncol.* 2014;32(34):3874-82.;
Fathi AT, et al. *Blood.* 2015;126:1328.;
Chevallier P, et al. *Haematologica.* 2017;102(5):e184-6.;
Chevallier P, et al. *Lancet Haematol.* 2015;2(3):e108-17.;
Olson NE, et al. *J Clin Oncol.* 2018 (suppl; abstract 7007).;
Bazarbachi AH, et al. *J Clin Oncol.* 2018 (suppl; abstract 7041).;
Passerini CG, et al. *J Clin Oncol.* 2018 (suppl; abstract 7062).

Role of New Agents in Treatment of Relapsed/Refractory ALL

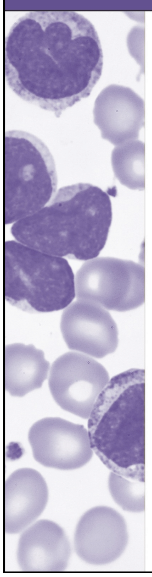


Relapsed disease (all comers)	Blinatumomab	Inotuzumab ozogamicin
MRD-positive disease in first or second remission	Blinatumomab	
Second or greater relapse	VSLI	Tisagenlecleucel*

*Up to age 25 years old

Blincyto [prescribing information]; 2018.; Marqibo [prescribing information]; 2016.; Besponsa [prescribing information]; 2017.; Kymriah [prescribing information]; 2018.

Pharmacist's Role in ALL



- ALL involves a highly specialized patient population
- Supportive care is critical to the survival of these patients, particularly during the induction phase when patients are aplastic for weeks
  - Antibiotics, antifungal, and transfusion support
- Risks of bleeding and infection inform all drug-therapy decision making
- Specific training and expertise required
  - Hematology/oncology, infectious diseases, general internal medicine, and critical care

Pedersen CA, et al. *Am J Health Sys Pharm.* 2011;68(8):669-688; Gamble KH. *Pharmacy Times.* 2011.

Pharmacist Provision of Direct Patient Care

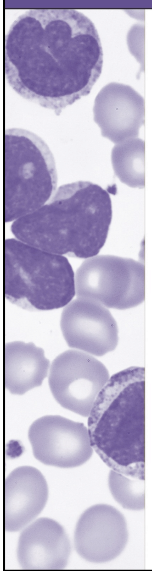
- Reduce medication errors and promote medication safety
- Ensure genomic/biomarker testing and recommend therapies that target specific genetic factors to avoid ineffective treatments
- Monitor/mitigate adverse events
- Provide patient education on toxicity, logistics for treatment regimens, and supportive care
- Educate the clinical team on new and emerging therapies

Pedersen CA, et al. *Am J Health Sys Pharm.* 2011;68(8):669-688; Gamble KH. *Pharmacy Times.* 2011.

Conclusions

- ALL efficacy results for adults continue to lag significantly behind pediatrics
- Progress with novel treatment options has been realized in the setting of relapsed/refractory ALL
  - VSLI, blinatumomab, inotuzumab ozogamicin, and tisagenlecleucel have generated modest but meaningful improvements in clinical outcomes for patients with ALL
  - These new agents require the expertise of pharmacists on the care team to ensure proper education for patients, mitigate serious toxicity, and provide appropriate supportive care

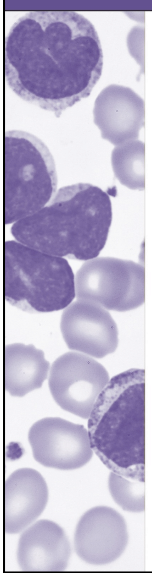
ARS Question #1



Which of the following best characterizes the general treatment strategy for patients with ALL?

A. A single cycle of multi-agent chemotherapy
B. Induction chemotherapy followed by allogeneic stem cell transplant for every patient
C. Induction chemotherapy followed by intensification and then maintenance therapy
D. Induction chemotherapy followed by maintenance therapy

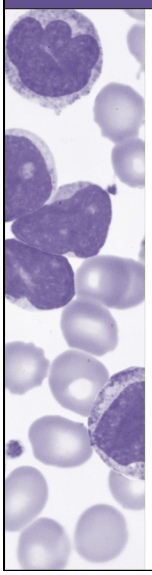
ARS Question #2



Which of the following represents the most appropriate use of liposomal vincristine sulfate injection?

A. Combination therapy with cyclophosphamide, doxorubicin, and prednisone for non-Hodgkin lymphoma
B. Use as an alternative to conventional vincristine formulation for grade 3 or worse neurotoxicity
C. Use in induction therapy for ALL with corticosteroids and L-asparaginase
D. Use as a salvage therapy for relapsed ALL patients with 2 or more prior antileukemic therapies

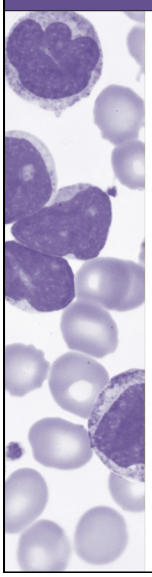
ARS Question #3



Which of the following ALL patient groups has been shown to benefit from chimeric antigen receptor T-cell therapy with tisagenlecleucel?

A. Patients with T-cell ALL
B. Patients with ALL who are older than 50 years of age
C. Patients of any age who are newly diagnosed with ALL
D. Patients aged 25 years or younger with B-cell ALL that has relapsed following conventional treatment

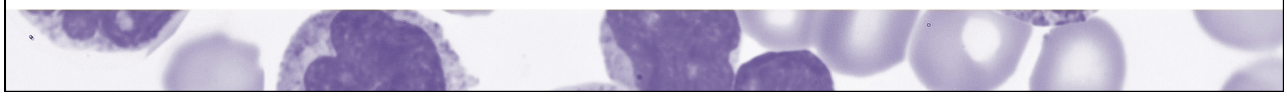
ARS Question #4



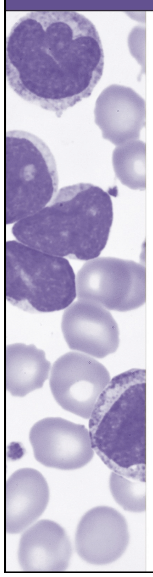
How could pharmacists be most beneficial to the care of patients being treated with inotuzumab ozogamicin?

A. Obtain prior authorization for treatment
B. Monitor at bedside for infusion-related toxicity during administration
C. Perform surveillance for changes in hepatic function and avoid use of concomitant hepatotoxic drugs
D. Assess appropriateness for hematopoietic stem cell transplant on the basis of donor availability

Questions and Answers



How to Claim Credit



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Thank You!