Pharmacology of Leukemia

Agents Used in Acute Myeloid Leukemia

Audra Andersen, PharmD, BCOP

Clinical Pharmacy Specialist

Miami Cancer Institute

Baptist Health South Florida

Objective

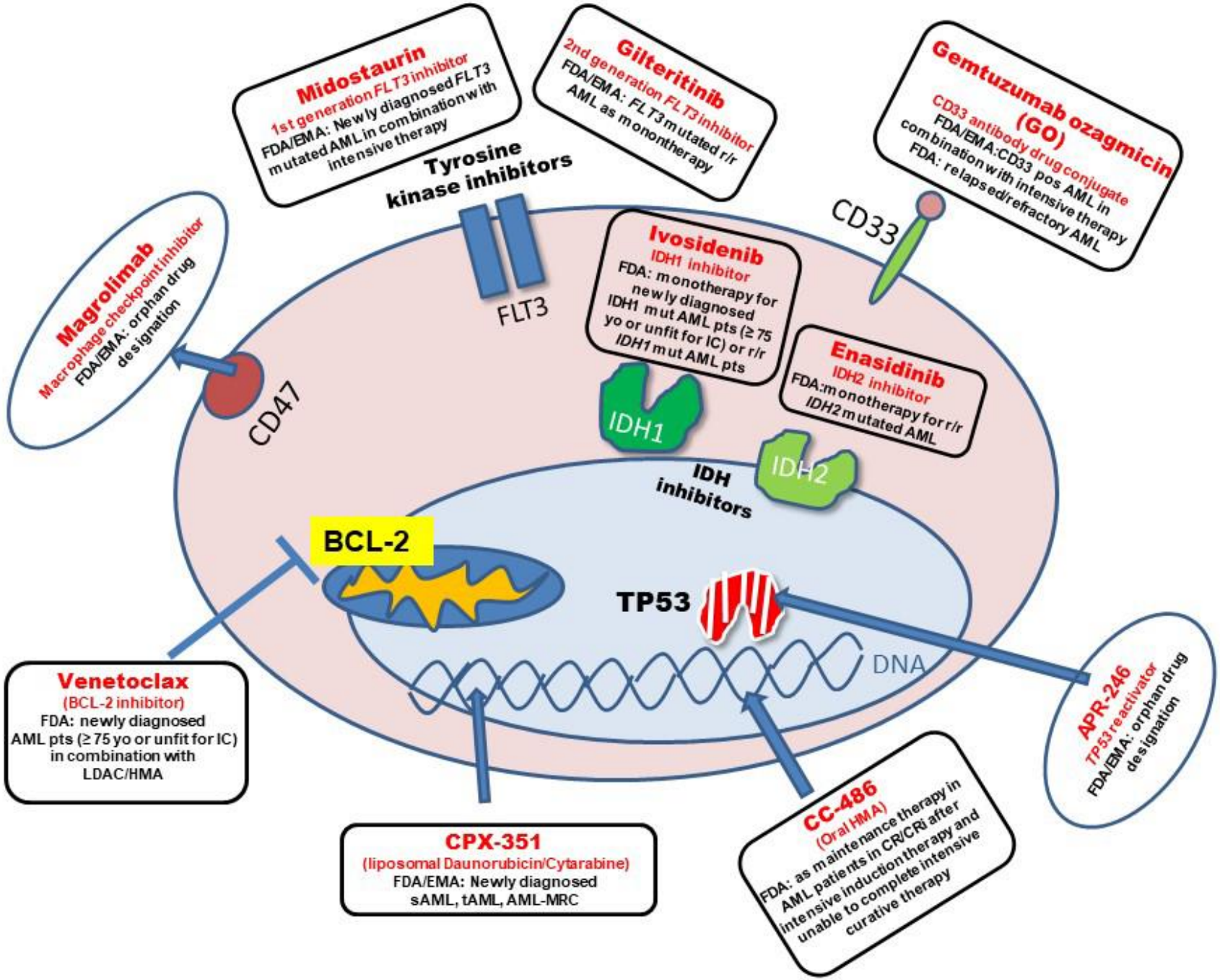
- Review key pharmacologic properties of medications used in the treatment of acute myeloid leukemia (AML)

Timeline of Treatment Approvals

1973	Cytarabine/ Daunorubicin (7+3)
1977	First bone marrow transplant

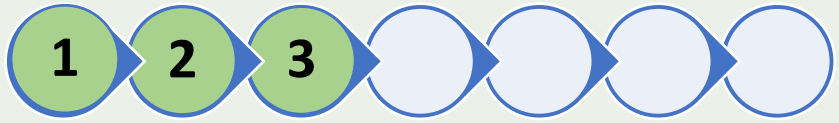
2000	Gemtuzumab ozogamicin
2002	Idarubicin
2010	Gemtuzumab ozogamacin withdrawn
2017	Gemtuzumab ozogamicin return, CPX-351, Enasidenib, Midostaurin
2018	Ivosidenib, Gilteritinib, Venetoclax, Glasdegib
2020	Azacitidine (oral)
2022	Olutasidenib

Carter, et al. *Signal Transduct Target Ther*. 2020;5(1):288.
Rowe JM. *Haematologica*. 2022;107(1):3.



Thol F. *Hematology Am Soc Hematol Educ Program*. 2021;2021 (1): 16–23.

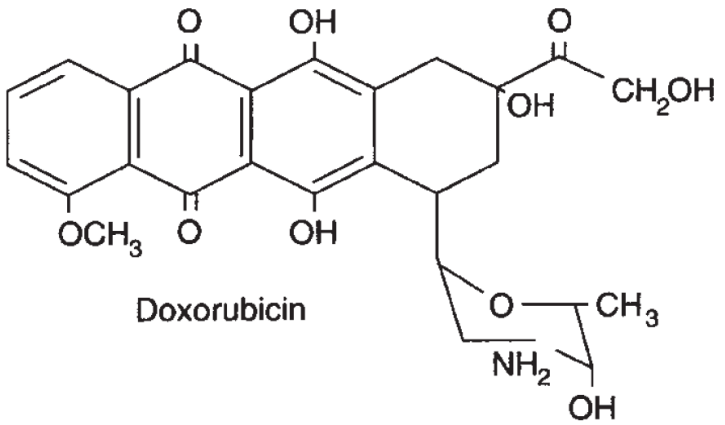
The “7+3” Regimen

Drug		Doses	Days	Delivery
Cytarabine		100 – 200 mg/m²		Continuous Infusion
Anthracyclines	Daunorubicin	45 – 90 mg/m²		Intravenous
	Idarubicin	12 mg/m²		Intravenous
	Mitoxantrone	12 mg/m²		Intravenous

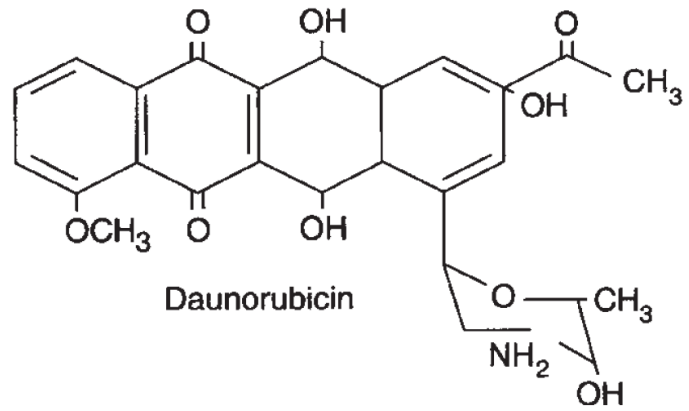
Yates, et al. *Cancer Chemother Rep*. 1973;57(4):485-488.
Fernandez, et al. *N Engl J Med*. 2009;361(13):1249-1259. Burnett et al. *Blood.* 2015;125(25):3878-85.
Vogler, et al. *J Clin Oncol*. 1992;10(7):1103-11. Pautas et al. *J Clin Oncol*. 2010;28(5):808-814.
Arlin, et al. *Leukemia*. 1990;4(3):177-183.

Anthracyclines

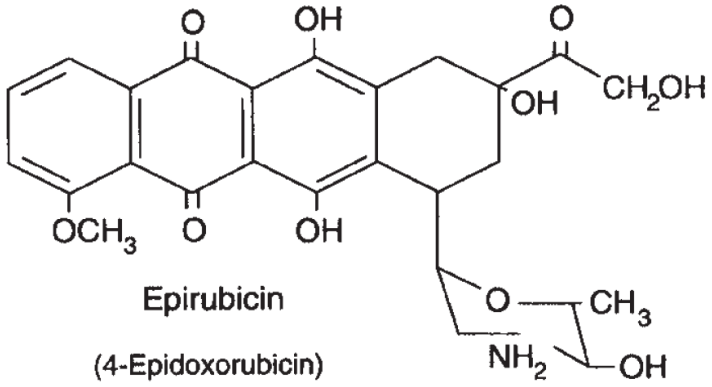
Mechanism of action: DNA intercalation, topoisomerase II inhibition, double-stranded DNA breaks, generation of free radicals



Doxorubicin

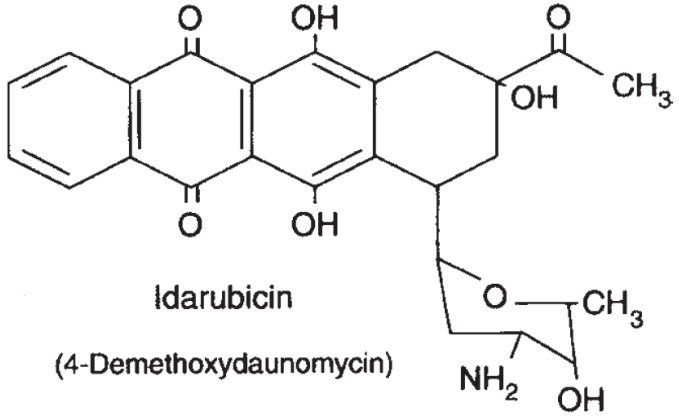


Daunorubicin



Epirubicin

(4-Epidoxorubicin)



Idarubicin

(4-Demethoxydaunomycin)

Doroshow. Topoisomerase II inhibitors: Anthracyclines. Chabner, B. A., & Longo, D. L. (Eds.). In: *Cancer Chemotherapy and Biotherapy: Principles and practice*. Wolters Kluwer Health;2011; 372-407.
Zamorano, et al. *Eur Heart J* 2016; 37:2768.

Anthracycline Adverse Effects

- Cardiotoxicity
- Myelosuppression
- Extravasation
- Urine, tear, saliva discoloration
- Alopecia

Cumulative dose (mg/m^2) associated with > 5% incidence of heart failure	
Daunorubicin	400
Daunorubicin/ Cytarabine Liposomal	400
Doxorubicin	450
Doxorubicin liposomal	550
Epirubicin	900
Idarubicin	90
Mitoxantrone	120

Doroshow. Topoisomerase II inhibitors: Anthracyclines. Chabner, B. A., & Longo, D. L. (Eds.). In: *Cancer Chemotherapy and Biotherapy: Principles and practice*. Wolters Kluwer Health;2011; 372-407.
Zamorano, et al. *Eur Heart J* 2016; 37:2768.

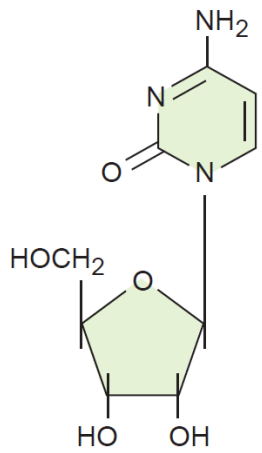
Anthracycline Dose Adjustments

	Renal Impairment	Hepatic Impairment
Daunorubicin	GFR 30 - 50 mL/min: 75% of the original dose GFR < 30 mL/min, HD: 50% of the original dose	Bilirubin 1.2 - 3 mg/dL: 75% of the original dose Bilirubin > 3 mg/dL: 50% of the original dose
Idarubicin	GFR ≥ 30 mL/min: No need for dose adjustment is expected GFR < 30 mL/min, HD: Consider 67% of the original dose	Bilirubin > ULN: Consider dose reduction Bilirubin 2.6 - 5 mg/dL: 50% of the original dose Bilirubin > 5 mg/dL: Not recommended
Mitoxantrone	No need for dose adjustment is expected	Mild/Moderate: No need for dose adjustment is expected Severe: Consider 50% of the original dose

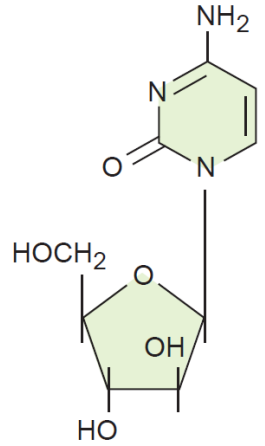
Krens, et al. *Lancet Oncol* 2019; 20: e200–07.

Cytarabine

Mechanism of Action: pyrimidine antimetabolite, inhibition of DNA polymerase, cell cycle specific for S phase



CYTIDINE



CYTOSINE ARABINOSIDE

Dose/Administration

Continuous Infusion (7+3)	100 – 200 mg/m^2 per day
High-dose (HiDAC) for consolidation	1500 – 3000 mg/m^2 IV over 3 hours every 12 hours on Days 1, 3, 5 (total 6 doses)
Low-dose (LoDAC) for low-intensity therapy (combination with venetoclax, glasdegib)	20 mg/m^2 SubQ daily on Days 1 – 10 20 mg SubQ BID Days 1 – 10

Mayer, et al. *N Engl J Med*. 1994;331(14):896-903.
Wei, et al. *Blood*. 2020;135(24):2137.
Chabner BA, Glass J. Cytidine Analogues. In: *Cancer Chemotherapy and Biotherapy: Principles and Practice*. Wolters Kluwer Health;2011; 372-407

Cytarabine Adverse Effects

- Cerebellar toxicity
  - Neurological assessments to evaluate for nystagmus, slurred speech, dysmetria
- Ocular toxicity
  - Drug-induced conjunctivitis; prevent and treat with corticosteroid eye drops every 6 hours until 48 hours after last dose of cytarabine
- Myelosuppression
- Gastrointestinal toxicity

Mayer, et al. *N Engl J Med*. 1994;331(14):896-903.
Wei, et al. *Blood*. 2020;135(24):2137.
Chabner BA, Glass J. Cytidine Analogues. In: *Cancer Chemotherapy and Biotherapy: Principles and Practice*. Wolters Kluwer Health;2011; 372-407

Cytarabine Dose Adjustments

	Renal Impairment	Hepatic Impairment
High-Dose ≥ 1000 mg/m²	GFR ≥ 60 mL/min: No adjustment necessary GFR 31 - 59 mL/min: 50% of the original dose GFR < 30 mL/min: Not recommended HD: 50% of the original dose	Mild/Moderate: No need for dose adjustment is expected Severe: Consider 25 - 50% of the original dose; increase if tolerated
Low-Dose	No adjustment necessary	No adjustment necessary
Continuous Infusion	No adjustment necessary	No adjustment necessary

Krens, et al. *Lancet Oncol* 2019; 20: e200–07.

Liposomal Daunorubicin and Cytarabine

Mechanism of Action: dual-drug liposomal encapsulation, fixed 1:5 (daunorubicin:cytarabine) molar ratio

Dose/Administration: 44 mg/m^2 of daunorubicin and 100 mg/m^2 of cytarabine IV over 90 minutes on Days 1, 3, and 5

Adverse Effects

- More prolonged neutropenia and thrombocytopenia than 7+3
- Lower rate of alopecia and gastrointestinal toxicity

Lancet, et al. *J Clin Oncol.* 2018;36(26):2684-2692.
Hematology Am Soc Hematol Educ Program (2021) 2021 (1): 16–23.

Liposomal Daunorubicin and Cytarabine Dose Adjustments

Renal Impairment	Hepatic Impairment
CrCl > 15 mL/min: No adjustment necessary HD: Not studied	Bilirubin ≤ 3mg/dL: No adjustment necessary Bilirubin > 3mg/dL: Not studied

Jazz Pharmaceuticals. Vyxeos [daunorubicin and cytarabine liposome injection, powder, lyophilized, for suspension]. Dailymed website. DailyMed - VYXEOS (- daunorubicin and cytarabine liposome injection, powder, lyophilized, for suspension (nih.gov) Revised [9/27/22]. Accessed [4/25/23].

Gemtuzumab Ozogamicin

Mechanism of Action: anti-CD33 antibody-drug conjugate, calicheamicin payload

Dose/Administration

Induction with 7+3:

3 mg/m^2 (maximum 4.5 mg) IV

over 2 hours on Days 1, 4, and 7

Adverse Effects

- Hepatotoxicity, veno-occlusive disease (VOD)/sinusoidal obstruction syndrome (SOS)
- Hypersensitivity/Infusion Reactions
  - Pre-medicate prior to each gemtuzumab ozogamicin dose with acetaminophen, diphenhydramine, and methylprednisolone
- Thrombocytopenia

Castaigne, et al. *Lancet*. 2012;379(9825):1508-16.

Gemtuzumab Ozogamicin Dose Adjustments

Renal Impairment	Hepatic Impairment
CrCl ≥ 30 mL/min: No adjustment necessary CrCl < 30 mL/min or HD: No need for dose adjustment is expected	Mild: No adjustment necessary Moderate/Severe: No need for dose adjustment is expected

Krens, et al. *Lancet Oncol* 2019; 20: e200–07.

FLT3 Inhibitors

Mechanism of Action: tyrosine kinase inhibitor, inhibits FLT3 receptor signaling and cell proliferation, and induces apoptosis in FLT3 expressing leukemic cells

Agent	Mechanism of Action	Generation
Sorafenib	Type II Targets ITD	First generation
Midostaurin	Type I Targets ITD and TKD	First generation
Gilteritinib	Type I Targets ITD and TKD	Next generation

Smith CC. *Hematology Am Soc Hematol Educ Program*. 2019;2019(1):539-547.
Antar, et al. *Leukemia*. 2020;34(3):682-696.

FLT3 Inhibitors

Dose/Administration

Midostaurin	**Induction:** 50 mg PO BID on Days 8 - 21 of each cycle (with 7+3) **Consolidation:** 50 mg PO BID on Days 8 - 21 of each 28-day cycle (with HiDAC) for 4 cycles
Gilteritinib	**Relapsed/Refractory**: 120 mg PO daily

Smith CC. *Hematology Am Soc Hematol Educ Program*. 2019;2019(1):539-547.
Antar, et al. *Leukemia*. 2020;34(3):682-696.

FLT3 Inhibitor Adverse Effects

Midostaurin

- Nausea, vomiting, diarrhea
- Interstitial lung disease/pneumonitis
- QTc prolongation
- Cytopenias

Gilteritinib

- Differentiation syndrome
- Posterior reversible encephalopathy syndrome
- AST/ALT elevations
- QTc prolongation
- Cytopenias

Wang ES, Baron J. *Hematology Am Soc Hematol Educ Program*. 2020;2020(1):57-66.

FLT3 Inhibitor Dose Adjustments

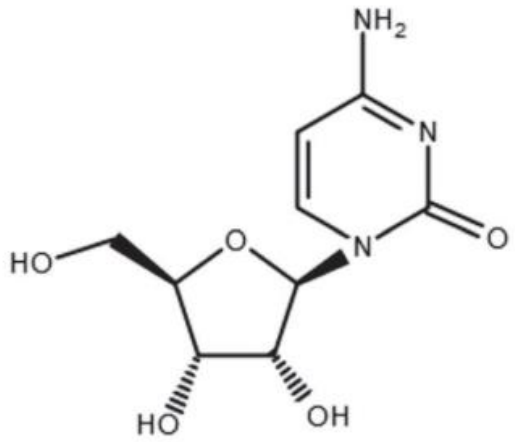
	Renal Impairment	Hepatic Impairment
Midostaurin, Gilteritinib	GFR ≥ 30 mL/min: No adjustment necessary GFR < 30 mL/min or HD: No need for dose adjustment is expected	Mild/Moderate: No need for dose adjustment is expected Severe: Not recommended, Not studied

Krens, et al. *Lancet Oncol* 2019; 20: e200–07.

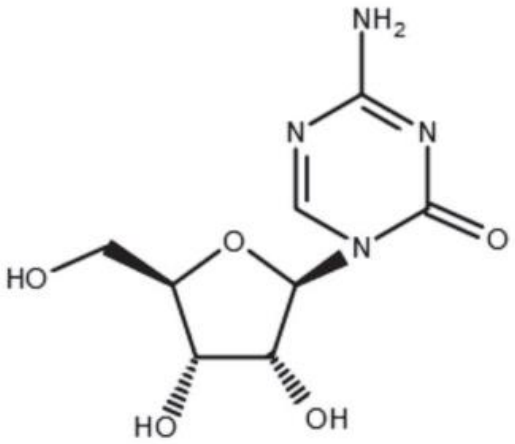
Hypomethylating Agents (HMAs)

Mechanism of Action: Analogs of nucleoside cytidine, incorporated into DNA/RNA, inhibits DNMT and induces DNA hypomethylation, trigger re-expression of genes that regulate tumor suppression

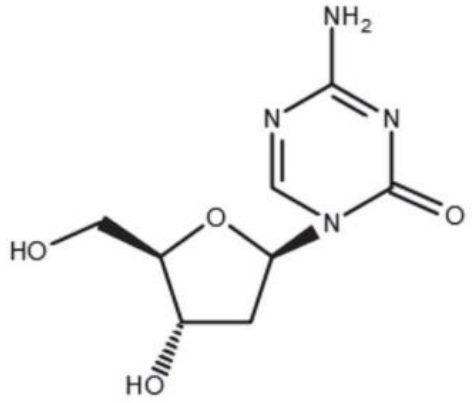
Cytidine



5-azacytidine



Decitabine



Stomper, et al. *Leukemia*. 2021;35(7):1873-1889.

Hypomethylating Agents (HMAs)

Dose/Administration

Azacitidine IV/SubQ	75 mg/m^2 on Days 1 – 7 of a 28-day cycle
Oral	Maintenance setting: 300 mg PO daily on Days 1 – 14 of 28-day cycle
Decitabine IV	20 mg/m^2 on Days 1 – 5 of 28-day cycle

Adverse Effects

- Anemia, thrombocytopenia, neutropenia, febrile neutropenia

Fenaux, et al. *J Clin Oncol*. 2010;28(4):562-9.

HMA Dose Adjustments

	Renal Impairment	Hepatic Impairment
Azacitidine IV/SubQ	No adjustment necessary	Mild/Moderate: No adjustment necessary Albumin <30 g/L: Use is not recommended
Azacitidine Oral	No adjustment necessary CrCl 15 - 29 mL/min: Monitor closely; adjust as needed	Mild: No adjustment necessary Moderate/Severe: Recommended dose adjustment has not been established; Not studied
Decitabine IV	No adjustment necessary HD: Not recommended	No need for dose adjustment is expected

Krens, et al. *Lancet Oncol* 2019; 20: e200–07.
Celgene. Onureg [azacitidine tablet, film coated]. Dailymed website. DailyMed - ONUREG- azacitidine tablet, film coated (nih.gov). Revised [10/26/22]. Accessed [5/4/23].

Venetoclax

Mechanism of action

- Selective inhibition of BCL-2 restores the apoptotic process

Dose/Administration

Ramp-up Phase with Azacitidine or Decitabine	Ramp-up Phase with LoDAC
100 mg PO on Day 1	
200 mg PO on Day 2	
400 mg PO on Days 3 - 28	600 mg PO on Days 3 - 28

DiNardo, et al. *N Engl J Med.* 2020;383(7):617-629.
AbbVie Inc. Venclexta [venetoclax tablet, film coated]. Dailymed website. DailyMed - VENCLEXTA- venetoclax kit VENCLEXTA- venetoclax tablet, film coated (nih.gov). Revised [6/15/22]. Accessed [5/4/23].

Venetoclax Adverse Effects

- Febrile neutropenia
- Leukopenia
- Anemia
- Thrombocytopenia
- Pneumonia
- Tumor lysis syndrome

Jonas BA, Pollyea DA. *Leukemia*. 2019;33(12):2795-2804.

Venetoclax Dose Adjustments

Renal Impairment	Hepatic Impairment	Drug Interactions CYP3A4 Inhibitors
No adjustment necessary	Mild/Moderate: No adjustment necessary Severe: 50% of the original dose	Strong CYP3A4 Inhibitor (Ex: posaconazole): 50 mg, 70 mg, 100 mg daily Moderate CYP3A4 Inhibitor (Ex: isavuconazole): 200 mg daily

Rausch, et al. *Blood*. 2019; 134 (Supplement_1): 2640.
AbbVie Inc. Venclexta [venetoclax tablet, film coated]. Dailymed website. DailyMed - VENCLEXTA- venetoclax kit VENCLEXTA- venetoclax tablet, film coated (nih.gov). Revised [6/15/22]. Accessed [5/4/23].

IDH Inhibitors

Mechanism of Action: inhibition of mutated isocitrate dehydrogenase (IDH) enzymes decreases 2-hydroxyglutarate (2-HG) “oncometabolite” levels, reduces abnormal hypermethylation, and restores myeloid differentiation

Agent	Mechanism of Action
Ivosidenib	IDH1 inhibitor
Olutasidenib	
Enasidenib	IDH2 inhibitor

Issa GC, DiNardo CD. *Blood Cancer J.* 2021;11(6):107.
Stein, et al. *Blood*. 2017 Aug 10;130(6):722-731.

IDH Inhibitors

Dose/Administration

Ivosidenib	500 mg PO once daily with or without food (do not administer with a high fat meal)
Olutasidenib	150 mg PO twice daily on an empty stomach
Enasidenib	100 mg PO once daily with or without food

Issa GC, DiNardo CD. *Blood Cancer J.* 2021;11(6):107.

IDH Inhibitors

Adverse Effects

- Hyperbilirubinemia
- QTc prolongation
- Thrombocytopenia
- Anemia
- Neutropenia
- Diarrhea

Differentiation Syndrome

- Dyspnea
- Hypoxia
- Pulmonary infiltrates
- Culture-negative fevers
- Rapid weight gain/edema
- Multi-organ dysfunction

Issa GC, DiNardo CD. *Blood Cancer J.* 2021;11(6):107.
Ali, et al. *Blood*. 2022;140 (Supplement 1):11763–11764.

IDH Inhibitor Dose Adjustments

	Renal Impairment	Hepatic Impairment
Ivosidenib	eGFR ≥ 30 mL/min/1.73m^2: No adjustment necessary eGFR < 30 mL/min/1.73m^2 or HD: Not studied	Mild/Moderate: No adjustment necessary Severe: Not studied
Olutasidenib	CrCl ≥ 30 mL/min: No adjustment necessary CrCl < 30 mL/min or HD: Not studied	Mild/Moderate: No adjustment necessary Severe: Not studied
Enasidenib	No adjustment necessary	Mild: No adjustment necessary Moderate: 50% of the original dose may be considered Severe: Not recommended

Krens, et al. *Lancet Oncol* 2019; 20: e200–07.
Rigel Pharamceuticals, Inc. Rezlidhia [olutasideninb capsule]. Dailymed website. DailyMed - REZLIDHIA- olutasidenib capsule (nih.gov). Revised [3/29/23]. Accessed [5/4/23].
Agios Pharmaceuticals, Inc. Tibsovo [ivosidenib tablet, film coated]. Dailymed website. DailyMed - TIBSOVO- ivosidenib tablet, film coated (nih.gov). Revised [5/12/22]. Accessed [5/4/23].

Questions?

Pharmacology of Leukemia
Agents Used in Acute Myeloid Leukemia

Audra Andersen, PharmD, BCOP

Clinical Pharmacy Specialist

Miami Cancer Institute

Baptist Health South Florida