IDH and FLT3 Inhibitors in Elderly Patients with Newly Diagnosed Acute Myeloid Leukemia

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Learning Objectives

1. Identify the role in therapy of IDH1, IDH2, and FLT3 inhibitor targeted therapy in newly diagnosed elderly AML patients
2. Describe the safety and efficacy of low intensity combination regimens for IDH1, IDH2, and FLT3 mutations in newly diagnosed elderly AML patients

Drug Abbreviations	Drug
AZA	Azacitidine
VEN	Venetoclax
IVO	Ivosidenib
ENA	Enasidenib
LDAC	Low-dose cytarabine
FLT3i	FLT3 Inhibitor
GIL	Gilteritinib
LIC	Low-intensity chemotherapy
TT	Triplet Therapy (LIC + VEN + FLT3i)
DT	Doublet Therapy (LIC + FLT3i)

Eastern Cooperative Oncology Group (ECOG) Performance Status

- Grade 0: Fully active, able to carry on all pre-disease performance without restriction
- Grade 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of light or sedentary nature
- Grade 2: Ambulatory and capable of all selfcare but unable to carry out work activities; up and about more than 50% of waking hours
- Grade 3: Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
- Grade 4: Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
- Grade 5: Dead

Classification of Response

- Complete response (CR): bone marrow blast (BMB) < 5%, ANC > 1 x 10^9 ,and platelet recovery > 100
- Complete response with incomplete hematologic recovery (CRi): all CR criteria with residual Neutropenia or thrombocytopenia
- Composite complete response (CRc): CR + CRi
- Partial remission (PR): Normalization of blood counts (as defined above) + decrease of blast to 5-25% and decrease for pretreatment bone marrow blast by 50%

- Overall response rate (ORR): collective response definition

Long-term Outcomes

- Overall Survival (OS): number of days from trial beginning/randomization to the date of death
- Event-Free Survival: number of days from trial beginning/randomization to disease progression, treatment failure, confirmed relapse, or death

Standard Dosing

- Azacitadine 75 mg/m^2 SubQ or IV for 7 days
- Decitabine 20 mg/m^2 IV for 5-10 days
- Venetoclax 400 mg PO daily for 28 days

IHD1 and IDH2 Inhibitors

	Ivosidenib	**Enasidenib**
Target of Action	IDH1	IDH2
NCCN Recommendation	R/R and newly diagnosed AML	R/R AML
Dose	500 mg PO once daily	100 mg PO once daily
Side Effects	GI, fatigue, arthralgia, dyspnea, QTc prolongation, differentiation syndrome	Hypocalcemia, hypokalemia, differentiation syndrome, hepatoxicity
Drug-Drug interaction	Major CYP3A4 (substrate)	Minor CYP1A2 (substrate)
Cost (AWP)	$33,600 per 28-day cycle	$33,040 per 28-day cycle
Monotherapy Response	CR+CRh 41%	CRc 21%

R/R: Relapse/refractory; AWP: Average wholesale price

IDH Inhibitor Summary

	Pollyea, et al (2020)[1] N=109	**Ivosidenib IDH1 (Montesino, et al 2022)[2] N=146**	**Enasidenib IDH2 (DiNardo, et al 2021)[3] N=101**
Intervention	VEN + AZA	IVO + AZA	Enasidenib + AZA
IDH1 CRc, n (%)	22 (66.7)	34 (47)	-
IDH1 CRc, n (%)	43 (86)	-	37 (54)
Median OS, months	24.5	24	22
Summary	Standard non-IDH inhibitor therapy	IVO + AZA > AZA for IDH1 mutation	Enasidenib + AZA > AZA for IDH2 mutations

IDH1 Mutation Recommendations:

1. Azacitidine + Venetoclax
2. Ivosidenib + Azacitidine
3. Ivosidenib monotherapy

IDH2 Mutation Recommendations:

1. Azacitidine + Venetoclax

2. Enasidenib + Azacitidine
3. Enasidenib monotherapy

FLT3 Inhibitors

	Midostaurin	Gilteritinib	Sorafenib	Quizartinib
Target of Action	TKD/ITD	TKD/ITD	ITD	ITD
NCCN Recommendation	Newly Diagnosed AML	R/R AML	AML	Not FDA approved
Dose	50 mg PO BID on days 8-21	120 mg PO once daily	400 mg PO BID	30-60 mg PO daily*
Side Effects	QT prolongation, pulmonary toxicity, pancreatitis, increased LFTs	Differentiation syndrome, pancreatitis, QT prolongation, increased LFTs	Increase risk of bleeding, cardiac infarction, hand-foot rash, GI perforation, hepatotoxicity, hypertension, QT prolongation	Nausea, vomiting, pyrexia, infections, QT prolongation
Drug-Drug Interaction	Major CYP3A4 (substrate)	Major CYP3A4 (substrate)	Major CYP3A4 (substrate)	?
Cost (AWP)	$11,928 per cycle	$28,812 per cycle	$23,520 per cycle	?

*Dose used in studies. R/R: relapse/refractory, AWP: average wholesale price

FLT3 Inhibitor Summary

	VIALE-A (2020)[4] N=29	Ohanian, et al (2017)[5] N=27	Wang, et al (2022)[6] N=123	Maiti, et al (2021)[7] N=25	Short, et al (2021)[8] N=26	Yilmaz, et al (2022)[9] N=87
Intervention	VEN + AZA	Sorafenib + AZA	Gilteritinib + AZA vs AZA	FLT3 inhibitor + Decitabine + VEN	Gilteritinib + VEN + AZA	Triplet therapy (LIC + VEN + FLT3 inhibitor) vs Doublet therapy (LIC + FLT3 inhibitor)
CR, %	-	44	16.2 vs 14.3	75	73	67 vs 32
OS, months	12.5	8.3	9.8 vs 8.9	NR at 2 years	-	NR at 12 months vs 9.5
CRc, %	72.4	57	58.1 vs 26.5	92	82	93 vs 70
Summary	Standard non-FLT3 inhibitor	NCCN Guideline FLT3 inhibitor	Terminated early	Increased overall survival	Increased response rate	Triplet therapy > doublet therapy

FLT3 Mutation Recommendations:

Azacitidine + Venetoclax

References

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