NEW COMBINATION DRUG REGIMENS USING HYPOMETHYLATING AGENTS IN TREATING OLDER PATIENTS WITH NEW DIAGNOSIS OF ACUTE MYELOID LEUKEMIA

PAVAN TENNETI MD, ANKITH TENNETI, SRINIVASA SANIKOMMU MD
LEVINE CANCER INSTITUTE, CHARLOTTE, NC

INTRODUCTION

- The prognosis of acute myeloid leukemia(AML) in older patients is inherently poor.
- In older patients not fit for intensive chemotherapy, complete response/complete response with incomplete hematologic response(CR/CRi) and median overall survival(mOS) has been evaluated with hypomethylating agents(HMA) including azacytidine(AZA)(CR/CRi=18-27.8%, mOS=10.4-24.5 m) and decitabine(CR/CRi= 18-47%, mOS= 7-7.8 m).
- The addition of venetoclax to HMA further improved CR/CRi(75%)and mOS(17.5 m).
- We conducted a systematic review of published literature to evaluate newer combination drug regimens (CDR) involving HMA from 2015-2020.

METHODS

- Comprehensive literature search was conducted in PubMed, Embase, and Cochrane databases.
- Phase I/II studies that used CDR along with a HMA were included in review.
- Initial database search lead to 1120 studies. Final analysis included 12 studies(n=655).

RESULTS

- In seven phase I/II studies, decitabine(n=500) was combined with gemcitabine ozagamicin (n=40, CR/CRi =45%, mOS= 7 m), cladribine and low dose cytarabine(n=118, CR/CRi= 68%, mOS =13.8 m), vadastuximab talirine(n=53, CR/CRi=70%, mOS=11.3 m) and selinexor(n=5, CR/CRi= 80%).
- Three studies compared outcomes of CDR involving decitabine with altrans retinoic acid(ATRA)(n=93, ORR=21.9% vs 13.5%, p=0.06; mOS= 8.2 m vs 5.1 m, p=0.006) or talacotuzumab(CR/CRi= 15% vs 11%, p=0.44; mOS= 5.36 m vs 7.26 m, p=0.78) or bortezomib(CR/Cri= 39% vs 38%, p=0.91, mOS=9.3 m vs 8.9,p=0.18) to decitabine alone.
- Cladribine and low dose cytarabine with decitabine in patients with adverse cytogenetics showed a decent CR/CRi of 50%, mOS= 10.5 months. In TP 53 positive mutations, CR/CRi was 40% and mOS was 5.4 months.
- Five phase I/II studies using CDR with AZA(n=155) were included in our review. Drugs included midostaurin(n= 88 , CR/CRi=25-29% mOS= 6-8 m) and pracinostat (n= 50, CR/CRi =46% mOS=19.1 m). In addition, two studies compared outcomes using CDR involving AZA with panobinostat(n=22, CR= 22.4 vs 30.8%, OS at 1 year = 60% vs 70%) or entinostat(n=18, ORR= 0% vs 16.6%, mOS=6 m vs 13 m) to AZA alone.

CONCLUSIONS

- Novel drug combinations involving decitabine including cladribine and low dose cytarabine, vadastuximab talarine showed superior CR/CRi and mOS compared to decitabine alone used in historic studies. In addition, CR/CRi were similar to HMA and venetoclax combination. In small number of patients, CDR with Selinexor also showed superior CR/CRi compared to decitabine alone. Decitabine and ATRA combination showed superior mOS in direct comparison with decitabine alone. In addition, cladribine and low dose cytarabine with decitabine has shown promising outcomes in patients with adverse cytogenetics.
- Among CDR involving AZA, even though pracinostat showed superior CR/CRi and mOS compared to AZA alone, this CDR was not efficacious in a recent phase III study.
- The above listed CDR involving decitabine need evaluation in large, randomized studies to assess for definitive benefit

TABLE- CDR USING HMA IN OLDER PATIENTS WITH AML

Author/year	Phase	HMA	Drug	Patient number	Response	RFS	OS
Daver et al. (2016)	II	D	GO (3 mg/m2)	40	CR/CRi=45%	NL	mOS=7 m
Kadia et al. (2018)	II	D	Cladribine (5 mg/m2) And Low dose cytarabine(20 mg subcutaneous bid)	118	CR/CRi=68%	mRFS= 10.8 m	mOS=13.8m
Roboz et.al (2018)	II	D	Bortezomib (1.3 mg/m2)	C=81 D=82	CR/CRi=39% vs 38%(p=0.91)	NL	mOS=9.3 m vs 8.9(p=0.18)
Fathi. et.al (2018)	I	D	Vadastuximab talirine (10ug/kg)	53	CR/CRi=70%	mRFS= 7.7m	mOS=11.3 m
Lubbart et.al.(2019)	II	D	ATRA D	C=46 D=47	ORR=21.9% vs 13.5(p=0.06)	NL	mOS=8.2 vs 5.1m(p=0.006)
Montesinos et.al(2020)	II	D	Talacotuzumab (9 mg/kg, n=80) D-20 mg/m2/d	C= 157 D=156	CR= 15% vs 11%(p=0.44)	mRFS=4.6 m vs 4.24 m	mOS=5.36 vs 7.26(p=0.78)
Bhatnagar et al(2020)	II	D	Selinexor (60 mg)	5	CR/CRi=80%	NL	NL
Garcia Monero et al.(2017)	IB/IIB	A	Panobinostat (20-40 mg)	C= 9 A=13	CR©-22.4% CR(A)-30.8%	NL	OS 1 yr- C-60% A-70%
Prebet et al (2016)	II	A	Entinostat (4 mg/m²/day day 1 and 10)	C=8 A=10	ORR w A=16.6% CR w C=0%	NL	mOS, A=13 m C=6 m
Cooper et al (2015)	I	A	Midostaurin (25-75 mg bid)	12	CR/Cri=25%	NL	mOS= 6 m
Garcia Monero et al.(2019)	II	A	Pracinostat (60 mg/day)	50	CR/Cri=46%	mRFS=12.6 m	mOS=19.1 m
Tomlinson et al.(2020)	II	A	Midostaurin (75 mg bid)	76	CR=29%	NL	mOS= 8 m

Abbreviations – A- Azacytidine, D- Decitabine, Mos= median overall survival, OS= Overall survival, ORR – Overall response rate, CR/Cri- complete response/complete response with incomplete hematologic recovery, mRFS- median event free survival,C= combination drug regimen, HMA – Hypomethylating agent, GO- Gemcitabine ozogamicin, m- months, NL- Not listed, ATRA- Altrans- retinoic acid