3-2020

Evaluation of acute myeloid leukemia induction regimens in elderly patients

Monica Tadros
Miami Cancer Institute, MonicaT@baptisthealth.net

Guenther Koehne
Baptist Health Medical Group; Miami Cancer Institute, guentherk@baptisthealth.net

Talia Zahra
Baptist Health Medical Group; Miami Cancer Institute, taliaz@baptisthealth.net

Moe Shwin
Miami Cancer Institute, moes@baptisthealth.net

Jessica Unzaga
Miami Cancer Institute, JessicaUn@baptisthealth.net

See next page for additional authors

Authors
Monica Tadros, Guenther Koehne, Talia Zahra, Moe Shwin, Jessica Unzaga, and Nicholas Chow

Evaluation of acute myeloid leukemia induction regimens in elderly patients with unfavorable risk cytogenetics that are candidates for intensive remission therapy

Monica Tadros, Pharm.D., BCPS; Guenther Koehne, M.D., Ph.D.; Talia Zahra, M.D.; Moe Shwin, Pharm.D., BCOP;
Nicholas Chow, Pharm.D., BCOP; Jessica Unzaga, Pharm.D., BCPS, BCOP
Miami Cancer Institute, Baptist Health South Florida, Miami, FL

Introduction

- Acute myeloid leukemia (AML) is characterized by proliferation of immature myeloid cells in the bone marrow and primarily affects older adults (median age of diagnosis of 69 years)[1]
- Guideline-based treatment options for AML depend on patients' age, performance status, and adverse features such as unfavorable cytogenetics or molecular markers, and comorbidities[1]
- Response and tolerability to standard AML therapy [7 days of cytarabine plus 3 days of an anthracycline (7+3)] is reduced in elderly patients; alternative treatment options include monotherapy with hypomethylating agents (HMA) such as azacitidine or decitabine, however, use of these agents alone are associated with poorer response rates [2]
- Venetoclax, an oral BCL-2 inhibitor, is FDA approved in combination with HMAs or low-dose cytarabine for the treatment of newly-diagnosed AML in adults 75 years or older, or patients with comorbidities that preclude the use of intensive induction chemotherapy[3,4]
- Venetoclax + HMAs has been associated with 61% complete remission (CR)/ complete remission with incomplete count recovery (CR_i) rates in treatment-naïve older adults[3,4]
- Guidelines support the use of venetoclax in combination with HMAs or low dose cytarabine for patients ages 60 and older with unfavorable risk cytogenetics that are candidates for intensive remission induction therapy[1]

Objective

Evaluate the outcomes of AML induction regimens in patients 60 years or older with unfavorable risk cytogenetics that are candidates for intensive remission induction therapy at a community hospital

Methods

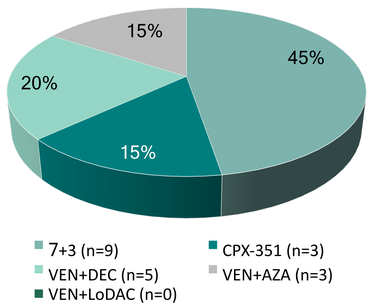
- **Design**: Single-center, IRB-approved, retrospective chart review
- **Evaluation period**: February 1st, 2018 - August 1st, 2019
- **Primary outcomes**: Rate of complete morphologic remission + complete morphologic remission with incomplete count recovery (CR/CRi)*
- **Secondary outcomes**: Rate of induction failure*, relapse free survival (RFS)*, time to CR/CRi, hospital length of stay (LOS), percentage of patients who went on to receive transplant, grade 1-5 treatment-related toxicities**
- **Inclusion criteria**: Age 60 or older at start of treatment, admitted to hospital oncology inpatient unit, confirmed AML diagnosis, unfavorable risk cytogenetics
- **Regimens studied**: cytarabine/daunorubicin (7+3 reference group); liposomal daunorubicin/cytarabine for therapy-related AML (CPX-351 reference group); venetoclax/decitabine (VEN+DEC); venetoclax/ azacitidine (VEN+AZA); venetoclax/low dose cytarabine (VEN+LoDAC)
- **Exclusion criteria**: Received prior therapy for AML
- **Procedure**: Patients identified using ICD 10 AML diagnosis codes; Fischer's exact test (categorical) and unpaired t test (continuous) used to determine statistical significance at an alpha of 0.05

*Outcomes defined by International Working Group response criteria for AML
**Toxicities graded using National Cancer Institute Common Terminology Criteria for Adverse Event [CTCAE] Version 5.0

Results

Patient Characteristics	N=20
Mean age, years	74
Age 60-74	45% (9)
Age 75+	55% (11)
Gender, female	50% (10)
Diagnoses	
• AML	50% (10)
• AML from MDS	50% (10)
Baseline ECOG status	
• 0	25% (5)
• 1	25% (5)
• 2	5% (1)
• Not documented	45% (9)

Regimens



Patient Characteristics	N=20
Mutations Found	
TP53	20% (4)
RUNX1	10%(2)
ASXL1	5% (1)
GATA2	10% (2)
FLT3	25% (5)
IDH1/2	20% (4)
NPM1	25% (5)
DNMT3A	40% (8)
STAG2	20%(4)
Del (7q)	10% (2)
Del (5q)	10% (2)
Del (17p)	10% (2)
Complex karyotype	40% (8)

Regimen	Rate of CR/CRi	Rate of induction failure	Median time to CR/CRi (days)	Median RFS (days)	Median LOS (days)	Transplant eligible	Received transplant
High Intensity (n=12)	**75% (9)**	**25% (3)**	**26**	**272**	**33**	**58% (7)**	**8% (1)**
• *7+3 (n=9)*	78% (7)	22% (2)	26	283	34	67% (6)	11% (1)
• *CPX-351 (n=3)*	67% (2)	33% (1)	32	530	40	33% (1)	0
Low Intensity (n=8)	**63% (5)**	**37% (3)**	**23**	**223**	**26**	**63% (5)**	**0**
• *VEN+DEC (n=5)*	60% (3)	40% (2)	25.5	184	29	60% (3)	0
• *VEN+AZA (n=3)*	67% (2)	33% (1)	23	357	17	67% (2)	0

Regimen	Median duration of neutropenia (days)	Median duration of thrombocytopenia (days)
High Intensity (n=12)	**30**	**31**
• *7+3 (n=9)*	27	23
• *CPX-351 (n=3)*	30	32
Low Intensity (n=8)	**34**	**32**
• *VEN+DEC (n=5)*	38	18
• *VEN+AZA (n=3)*	30	38

Treatment-related toxicities	High intensity (n=12)	Low intensity (n=8)
Any-grade toxicities	100% (12)	88% (7)
Grade 3/4 toxicities	100% (12)	88% (7)
Grade 3 FN	92% (11)	75% (6)
Grade 4 thrombocytopenia	92% 11)	88% (7)
Grade 1/2 AST or ALT increase	42% (5)	25% (2)
Grade 1/2 SCr increase	8% (1)	0
Grade 3 cardiotoxicity	8% (1)	0

Outcome	High intensity (n=12)	Low Intensity (n=8)	P value
CR/CRi rates	75%	63%	0.0922 (NS)
Median RFS	272 days	223 days	0.1496 (NS)
Grade 3/4 toxicities	100%	88%	0.0003

FN = febrile neutropenia
NS = not significant

Discussion

Observations:

- There was no statistically significant difference between the CR rates and RFS of the high and low intensity groups
- Significantly less grade 3/4 toxicities noted in low intensity group when compared to high intensity
- Rate of CR/CRi in venetoclax + HMA study cohorts is similar to those reported in studies
- Febrile neutropenia was the most commonly observed toxicity in all groups followed by grade 4 thrombocytopenia
- 2 patients were lost to follow up

Limitations of study design:

- Single center study
- Retrospective study creates potential for selection bias
- Lack of thorough documentation in the electronic medical record, particularly as is relates to baseline ECOG status and determining if toxicities were treatment-related or disease-related
- Low volume of patients due to extensive inclusion/exclusion criteria and inconsistent number of patients per treatment group prevents meaningful comparison between individual groups
- Unable to assess adherence to oral therapies (venetoclax) and determine effect of potential drug-drug interactions
- Provider utilization of decitabine 5-day vs. 10-day regimen not standardized
- Short duration of follow up (ongoing)

Conclusion

In this review, CR rates among the different regimens recommended for elderly AML patients were comparable, with more toxicities being observed with the more intensive regimens containing anthracyclines. Further larger studies are needed to be able to more accurately compare the regimens in terms of efficacy and toxicity.

Disclosures

All authors of this presentation have nothing to disclose concerning possible financial or personal relationships with commercial entities that may have direct or indirect interest in the subject matter of this presentation.

References

1. National Comprehensive Cancer Care Network. Acute Myeloid Leukemia (Version 3.2019).
2. DiNardo CD, Pratz K, Pullarkart V, et al. Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia. Blood. 2019 Jan 3;133(1):7-17.
3. Bell JA, Galaznik A, Farelly E, et al. A retrospective study evaluating treatment patterns and survival outcomes in elderly patients with acute myeloid leukemia treated in the United States with either 7+3 or a hypomethylating agent. Leuk Res. 2019 Mar;78:45-51.
4. Campos EDV, Pinto R. Targeted therapy with a selective BCL-2 inhibitor in older patients with acute myeloid leukemia. Hematol Transfus Cell Ther. 2019 Apr - Jun;41(2):169-177.
5. Knight T, Edwards H, Taub JW, Ge Y. Evaluating venetoclax and its potential in treatment-naïve acute myeloid leukemia. Cancer Manag Res. 2019 Apr 23;11:3197-3213.
6. https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf. Accessed July 30th, 2019.
7. Das M. Venetoclax with decitabine or azacitidine for AML. Lancet Oncol. 2018 Dec;19(12):e672.
8. Wei AH, Strickland SA, Hou JZ, et al. Venetoclax Combined With Low-Dose Cytarabine for Previously Untreated Patients With Acute Myeloid Leukemia: Results From a Phase Ib/II Study. J Clin Oncol. 2019 May 20;37(15):1277-1284.