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

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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).3
• Guideline-based treatment options for AML depend on patients’ age, performance status, and adverse features such as unfavorable cytogenetics or molecular markers, and comorbidities.6
• 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 (HMAs) such as azacitidine or decitabine, however, use of these agents alone are associated with poorer response rates.1
• 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.4,5
• Venetoclax + HMAs has been associated with 61% complete remission (CR)/complete remission with incomplete count recovery (CRi) rates in treatment-naive older adults.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 therapy1

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 (CRi/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 AML 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 EOCG status
• 0 25% (5)
• 1 25% (5)
• 2 5% (1)
• Not documented 45% (9)

Regimens

Rate of CR/CRI
75% (9) 25% (3)

Median time to CR/CRI (days)
26 272 33 58% (7) 8% (1)

Rate of induction failure
75% (10) 25% (5)

Median RFS
30 272 33 58% (7) 8% (1)

Median Los (OS)
30 272 33 58% (7) 8% (1)

Transplant eligible
30 272 33 58% (7) 8% (1)

Received transplant
30 272 33 58% (7) 8% (1)

Regimen

High intensity (n=12): 30
• 7+3 (n=9)
• CPX-351 (n=3)

Low intensity (n=8):
• VEN+DEC (n=5)
• VEN+AZA (n=3)

Gender
60% (7) 40% (2)
Male
63% (8) 37% (1)
Female
88% (10) 12% (1)

Age
75% (9) 25% (3)

Median duration of neutropenia (days)
20 272 33 58% (7) 8% (1)

Median duration of thrombocytopenia (days)
20 272 33 58% (7) 8% (1)

Treatment-related toxicities

Any-grade toxicities
100% (12)

Grade 3 toxicities
88% (10)

Grade 4 toxicities
42% (5)

Grade 3/4 toxicities
25% (2)

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 more accurately compare the regimens in terms of efficacy and toxicity.

Discussions

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 it relates to baseline EOCG 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)

References

7. Das M. Venetoclax with decitabine or azacitidine for AML. Lantet Oncol. 2018 Dec;19(12):6672.