

Abstract

BACKGROUND AND AIM

Recent FDA approvals of novel therapies and hypomethylating agents / venetoclax has transformed therapy of newly diagnosed older patients with AML. While achievement of complete remission (CR) has been the gold standard for AML response, novel therapies with different response dynamics warrant re-evaluation of response criteria. CR with partial hematological recovery (CRh, bone marrow blasts $\leq$ 5%, ANC $>$ 0.5×10^9 /L **and** platelet count $>50 \times 10^9$ /L) has been employed as a surrogate marker for efficacy and clinical benefit. We evaluated the impact of CRh on long-term outcomes of older pts with newly diagnosed AML treated with 10-day decitabine and venetoclax (DEC10-VEN, NCT03404193).

METHOD

Patients with newly diagnosed AML ages >60 years, or secondary AML were included. Patients received decitabine 20 mg/m² IV for 10 days with oral venetoclax 400 mg daily for induction and decitabine for 5 days with daily venetoclax for consolidation. Definitions of best response were as following: CR (Bone marrow blasts $\leq$ 5% blasts, absence of circulating blasts and blasts with Auer rods, absence of extramedullary disease and ANC $>$ 1×10^9 /L with platelet count $>100 \times 10^9$ /L), CR with incomplete hematologic recovery, CRi (All CR criteria but with residual cytopenia such as ANC $<$ 1×10^9 /L or platelet count $<100 \times 10^9$ /L) and morphological leukemia free state, MLFS (CR criteria without hematologic recovery). Outcomes of interest included overall survival (OS) and event-free survival (EFS). Full study protocol and interim results have been published previously (DiNardo et al. Lancet Haematol. 2020;7:e724-36.)

RESULTS

From January 2018 - February 2021 125 patients with a median age of 71 yrs (range 48-89) were included. 79 (63%) pts were newly diagnosed AML and 46 (37 %) had secondary AML with antecedent hematological disorder (**Figure 1**). 69 patients achieved CR (55%), 11 (8%) pts achieved CRh, 14 (11%) pts achieved CRi, 10 (8%) pts achieved MLFS and 21 (17%) pts were refractory. Of the 11 pts who met the criteria for CRh, 8 (73%) patients were previously classified as CRi and 3 (27%) as MLFS. Among 69 pts achieving CR, the median OS was 24.5 months (mo) and median EFS was 18.0 mo. CRh was achieved with a median of 1 (range 1-3) cycles. Median OS of CRh as compared to CRi was 16.9 vs 5.8 mo (HR 0.47, 95% CI 0.19-1.13, p=.06) and CRh vs MLFS was 16.9 vs 6.2 mo (HR 0.34, 95% CI 0.13-0.93, p=.007). Median EFS of pts with CRh vs CRi was 14.1 vs 5.8 mo (HR 0.49, 95%CI 0.21-1.14, p=.08) and CRh vs MLFS was 14.1 vs 6.2 mo (HR 0.37, 95% CI 0.14-1.01, p=.016). Pts achieving CRh defined a group with durable remission with duration of response of 6.0 vs 2.5 mo with CRi and 1 mo with MLFS. Additional analyses are ongoing and will be presented.

CONCLUSION

In pts with newly diagnosed AML and secondary AML treated with DEC10-VEN, pts achieving CRh had a trend towards improved OS and EFS compared to pts with CRi or MLFS. These findings support the use of CRh as an endpoint demonstrating clinical benefit for patients receiving venetoclax-based therapy. Larger analyses are warranted.

Background

- HMAS & Venetoclax are the standard of care in newly diagnosed older patients in AML
- ELN 2017 response criteria currently includes complete remission (CR), CR with incomplete hematologic recovery (CRi), Morphologic leukemia-free state (MLFS) and Partial remission (PR)
- Advent of novel therapies requires reassessment of response criteria, with inclusion of CR with partial hematological recovery (CRh, bone marrow blasts $<$ 5%, ANC $>$ 0.5×10^9 /L and platelet count $>50 \times 10^9$ /L) as a marker for efficacy and clinical benefit

Objective

- Impact of CRh on overall survival (OS) and event free survival (EFS) of older pts with newly diagnosed AML treated with 10-day decitabine and venetoclax

Materials & Methods

Eligibility

- ND AML (>60 yrs), R/R AML, sAML
- WBC $\leq 10 \times 10^9$ /L

Excluded

- Favorable risk cytogenetics – APL, CBF, AML
- Prior BCL2 inhibitor therapy

Treatment

- DEC 20 mg/m² x 10 days every 4-8 weeks
- Consolidation/maintenance: DEC x5D post CR/CRi
- VEN D1-28 for cycle 1 → D1-21 cycle 2 onward
- If C1D21 BM showed $<5\%$ blasts → VEN held for count recovery
- Further reduction of VEN duration allowed for myelosuppression
- Inpt admission - ND pts - C1 of VEN, R/R pts - 3 days of VEN dose escalation

Materials & Methods (contd)

- VEN dose reduced by 50-75% with CYP3A4i (e.g. azoles)
- Targeted therapies allowed - FLT3i, BCR-ABL TKIs
- TLS prophylaxis
- Treatment discontinued if progression or no response after ≥ 4 cy

Response Assessment

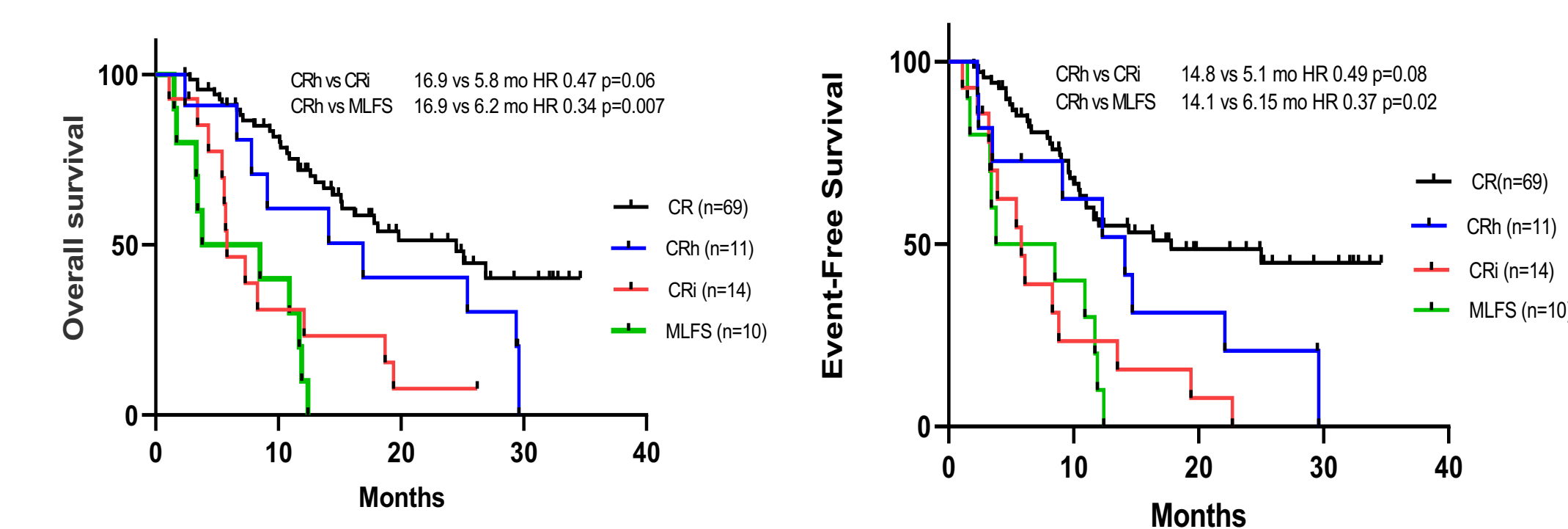
- CR - Bone marrow blasts $\leq 5\%$ blasts, absence of circulating blasts and blasts with Auer rods, absence of extramedullary disease and ANC $>$ 1×10^9 /L with platelet count $>100 \times 10^9$ /L,
- CR with partial hematological recovery (CRh, bone marrow blasts $\leq 5\%$, ANC $>$ 0.5×10^9 /L **and** platelet count $>50 \times 10^9$ /L)
- CR with incomplete hematologic recovery, CRi (All CR criteria but with residual cytopenia such as ANC $<$ 1×10^9 /L or platelet count $<100 \times 10^9$ /L)
- Morphological leukemia free state, MLFS (CR criteria without hematologic recovery)

Table 1, baseline characteristics

	n (%) median (range)
Patients	125
Age, years	71 [48-89]
Male sex	70 (56)
White blood cell count, $\times 10^9$/L	2.9 [0.3-25.5]
ECOG PS	0 - 17 1- 72 >2 - 36
Bone marrow blasts %	37.5% [2-90%]
Diagnosis	De novo -79 (63) Untreated sAML with AHD – 20 (16) Treated sAML with AHD – 26 (21)
Mutations	<i>NPM1</i> – 27 <i>FLT3 ITD or TKD</i> – 21 <i>TP53</i> – 38 <i>RUNX1</i> – 20 <i>IDH1</i> – 10 <i>IDH2</i> - 19 <i>K/NRAS</i> - 28
ELM 2017 cytogenetic risk	Intermediate - 51 Adverse - 36 Insufficient metaphases - 1

Results

- At time of response assessment, CR - 69 patients (55%), CRh - 11 (8%) , CRi -14 (11%), MLFS -10 (8%), refractory 21 (17%)
- Of 11 CRh patients, 8 (73%) patients were previously CRi, 3 (27%) as MLFS
- **Overall Survival** CR vs CRh vs CRi vs MLFS 24.5 vs 16.9 vs 5.8 vs 6.2 months
- **Event Free Survival** CR vs CRh vs CRi vs MLFS 18 vs 14.8 vs 5.1 vs 6.15 months
- **Duration of response** CRh vs CRi vs MLFS 6.0 vs 2.5 vs 1 month



Conclusion

- Patients who were re-classified as CRh from CRi or MLFS showed improved trend of overall survival and event free survival
- CRh needs to be evaluated in larger studies as an end marker for clinical efficacy and eventually cause reassessment of response criterial in AML given the advent of newer therapies

Disclosures

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Clinical trial registration: NCT03404193