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# P523 THE COMPARISON OF VFLAI, FLAI AND 3+7 REGIMENS BY MULTILEVEL PROPENSITY SCORE WEIGHTING HIGHLIGHTS THE BENEFIT OF THE ADDITION OF VENETOCLAX IN NO LOW-RISK AML TREATED IN GIMEMA TRIALS AND REAL WORLD

**Topic:** 4. Acute myeloid leukemia - Clinical

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**Background:**

Venetoclax combined with intensive chemotherapy proved to be safe with promising activity in fit patients with no-low-risk newly diagnosed acute myeloid leukemia (AML), as demonstrated by an interim analysis of the GIMEMA AML1718 trial. The GIMEMA AML1718 trial was based on the administration of venetoclax-FLAI (V-FLAI) to intermediate/high-risk ELN2017 AML and produced a complete remission (CR) rate of 84%, a minimal residual disease (MRD)-negativity rate of 74% and a 12-month Overall Survival (OS) and Disease-free survival (DFS) of 75.7% and 80.7%.

**Aims:**

In order to evaluate the actual advantage of the addition of venetoclax to chemotherapy, the AML1718 was compared to AML1310 - which entailed a "3+7"-like induction and a risk-adapted, MRD-directed post-remission transplant allocation (Venditti et al. 2019)-, and to FLAI real-life single center experience (Guolo et al. 2016), which entailed a FLAI therapy.

**Methods:**

To generate a reliable comparison, patient-level data from AML1718 (n=57), AML1310 (n=445) and real-life experience (n=155) with ELN2017 risk classification available were used to conduct a multilevel propensity score weighting analysis, widely used for reducing the effects of confounding when estimating the effects of treatment on outcomes. Since age, gender, ELN2017 risk and allogenic transplant rate differed among the 3 cohorts, these variables were included in the propensity score. Being more recent, AML1718 median follow-up was shorter than both AML1310 and FLAI treatment (10.5 vs 75.8 vs 104.8 months). A variety of balancing weights were attempted: inverse probability of treatment weights, overlap weights, matching weights and entropy weights. For determining adequate balance, the diagnostic method employed was the standardized mean difference (SMD). A standardized bias score less than 0.2 was used as a criterion for adequate balancing. Weights were calculated with a multinomial logistic regression model. Odds Ratio (OR) were estimated using logit models.

**Results:**

The matching weights produced the best balance, with SMDs <0.18 for all variables. The final weighted sample sizes on which the analysis has been carried out were 183 (3+7), 54 (V-FLAI) and 155 (FLAI). After weighting

(Table 1), the CR rate observed in the V-FLAI group was higher than FLAI and 3+7, as well as MRD-negativity rate. In terms of OR the probability of achieving CR in V-FLAI and FLAI patients was significantly higher compared to 3+7 patients (p=0.01 and p=0.03, respectively). Contrariwise, comparing V-FLAI and FLAI, the CR probability did not differ significantly (p=0.34). With regards to MRD, the V-FLAI group had a higher probability of achieve MRD-negativity than both FLAI and 3+7 treatments (p=0.005 vs FLAI; p=0.001 vs 3+7). Upon weighting, DFS and OS estimates of the V-FLAI group were higher than the other two, though a slight statistical significance was reached only on DFS (p=0.048, Table 1). However, a longer AML1718 follow-up is needed to provide a robust comparison.

**Summary/Conclusion:**

Our propensity-score weighting analysis showed that combining venetoclax with chemotherapy in newly diagnosed AML patients resulted in improved outcomes compared to FLAI therapy and to 3+7 regimen in terms of MRD-negativity. In terms of CR, venetoclax-based therapy was preferable only to 3+7 scheme. With regards to survival outcomes, a solid conclusion will be drawn when a longer AML1718 follow-up is available. These preliminary results highlight the incremental benefit of venetoclax added to intensive induction chemotherapy and paves the way to novel combination regimens.

**Table 1.** Comparison of characteristics and outcomes of V-FLAI, FLAI and 3+7 patients after weighting using propensity score method.

| | *V-FLAI vs FLAI vs 3+7 comparison* | | | | *Pairwise comparisons* | |
|---|---|---|---|---|---|---|
| | **V-FLAI, N = 54** | **FLAI, N = 155** | **3+7, N = 183** | ***P*** | **OR** | ***P*** |
| **Patients' characteristics** | | | | | | |
| **Age, median (range)** | 51 (18, 66) | 50 (17, 75) | 50 (18, 61) | 0.99 | | |
| **Males, n (%)** | 39 (72%) | 88 (57%) | 113 (62%) | 0.98 | | |
| **Graft, n (%)** | 29 (54%) | 68 (44%) | 90 (49%) | 0.99 | | |
| **ELN2017 High Risk, n (%)** | 28 (51%) | 55 (35%) | 79 (43%) | 0.98 | | |
| **Response evaluation** | | | | | | |
| **CR, n (%)** | 48 (84%) | 124 (80%) | 159 (63%) | **<0.001** | V-FLAI vs FLAI: 0.36 | 0.34 |
| | | | | | V-FLAI vs 3+7: 0.91 | **0.01** |
| | | | | | FLAI vs 3+7: 0.55 | **0.03** |
| **MRD- (<0.1%), n (%)** | 28 (74%) | 59 (48%) | 44 (40%) | **0.002** | V-FLAI vs FLAI: 1.18 | **0.005** |
| | | | | | V-FLAI vs 3+7: 1.40 | **0.001** |
| | | | | | FLAI vs 3+7: 0.22 | 0.48 |
| **Survival outcomes, estimate (95%CI)** | | | | | | |
| *12 months-OS* | 75.7% (64.1%, 89.5%) | 64.4% (57.2%, 72.4%) | 66.3% (60.7%, 72.4%) | 0.39 | | |
| *12 months-DFS* | 80.7% (67.9%, 95.9%) | 53.3% (46.0%, 61.8%) | 62.2% (55.0%, 70.4%) | **0.048** | | |



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