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## FLAI induction regimen in elderly patients with acute myeloid leukemia

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## **High efficacy and low mortality rate of fludarabine-based induction regimen in elderly AML patients**

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Prognosis of elderly acute myeloid leukemia (AML) patients remains dismal with less than 15-20% of long-term survivors. Though challenged by hypomethylating agents (HMA), intensive chemotherapy (IC) represents a valid option for fit patients and the “3+7” combination is still regarded as standard of care (1). The addition of fludarabine to cytarabine increases intracellular levels of its active metabolite Ara-CTP and was shown effective in the relapse setting (2). Moreover, although associated with increased toxicity, FLAG-ida (fludarabine/cytarabine/granulocyte-colony stimulating factor and idarubicin) showed higher anti-leukemic activity compared to standard induction in younger treatment-naïve AML patients (3). Data on this combination in the elderly are scanty (4) and randomized trials have not been performed. Here, we retrospectively report on our experience with FLAI (fludarabine 25-30 mg/m<sup>2</sup> days 1-5, cytarabine 1.5-2gr/m<sup>2</sup> days 1-5 and idarubicine 10 mg/m<sup>2</sup> days 1,3,5) in older patients. Since January 2002, 192 patients with AML (92%) or with higher IPSS Risk-Myelodysplastic Syndromes (8%) aged over 60 years and eligible for IC were treated with FLAI. Dose reductions by 20% (4-day regimen, FLAI-4) or 40% (3-day regimen, FLAI-3) were applied according to age and comorbidities. Patients who achieved complete remission (CR) received 1 or 2 consolidation courses and/or allogeneic hematopoietic stem cell transplantation (allo-HSCT). Patients not eligible for allo-HSCT could receive low dose cytarabine (LDAC)-based maintenance treatment. Cytogenetics, molecular classification and response evaluation were reported by the ELN 2010 recommendations. Fisher’s exact and Mann–Whitney rank-sum test were used to analyze categorical and continuous variables respectively. Survival analysis was carried out by the Kaplan–Meier method and log-rank tests and proportional hazard Cox models were used in uni- and multivariate models to assess impact of clinical (age, sex, secondary or therapy-related disease, dose reductions) and genetic (karyotype, *NPM1* and *FLT3* mutational status, ELN risk) variables on outcomes.

Patient median age was 67 years (range 60-79); 54% were male, 42% had secondary or therapy-related disease, 27% adverse karyotype and 66% were treated with reduced doses. Early death (ED) rate was 4.2 % and 7.3 % by day 30 and 60, respectively, and appeared higher in patients  $\geq 70$  years (8% vs.1.7%,  $p=0.058$ ; and 12% vs. 4.3%,  $p=0.052$ ). One hundred and fifteen patients (60%) obtained CR after induction. CR could be achieved after different salvage treatments in 8 additional patients. By univariate analysis, dose-reduced FLAI, age and adverse karyotype were associated with a lower probability of reaching CR whereas by multivariate analysis only age was significantly associated with CR ( $p=0.014$ ). Most patients in CR received at least one (89.3%,) or two (47.5%) intensive consolidation

cycles. Overall, 42 patients (34.4%) were further treated with LDAC-based maintenance. Twenty-six patients received allo-HSCT in first CR (21.3%); they were younger (median age 63 vs. 68 years,  $p=0.0001$ ) and mostly diagnosed after January 2010 (88.5%). After a median follow-up of 59.9 months, median overall survival (OS) was 13.0 months while OS at 2 and 5 years was 32.7% (95% CI, 26-39.5%) and 19.6% (95% CI, 13.6-26.9%) respectively (Figure 1). By univariate analysis, male sex, dose-reduced FLAI and adverse karyotype were associated with worse OS while *NPM1* mutations predicted better survival (median OS 19.9 vs. 12.6 months,  $p=0.023$ ). Age (as continuous variable) predicted worse OS, and patients  $\geq 70$  years had a median 2 year-OS of 24.4% vs. 38.2% in younger patients ( $p=0.0007$ ). By multivariate analysis, however, only age, male sex and adverse karyotype were significant. Overall, 74 patients relapsed from CR and 11 died in CR, for a 5-year disease free survival (DFS) of 27.2% (95%CI, 18.8-36.2%). Age and male sex were risk factors for worse DFS by multivariate analysis.

In our real-life experience, FLAI was associated with an encouraging 30-day and 60-day ED rate of less than 10% and a high CR rate of 60%. OS, although not yet satisfactory, compared favorably with most reports in this age group. FLAI regimens may overall improve results in secondary and poor-risk AML patients (2), who were highly represented in our cohort. Moreover, promising findings (CR rate 53.5%, median OS 12.6 months) were also observed in the group with adverse karyotype. Interestingly, 47% of our patients met the criteria to receive CPX-351, recently approved for secondary, therapy-related AML, and AML with myelodysplasia-related changes. Taking into account all the methodological limitations of such a comparison, our findings are similar to those achieved with CPX-351 (CR rate 54.4% vs. 47.7%, 2 year OS 33.3% vs. 31.1%) (5). Even though some conflicting data have been reported (6), *NPM1*-mutated AML is usually associated with favorable prognosis and our results confirm the efficacy of FLAI in this setting (CR rate 74%, median OS 20 months), as reported by others in younger patients(7,8). FLAI dose adjustments were made in 60% of our patients in the light of previous findings (4). However, dose reduction was not associated with inferior outcomes by multivariate analysis and age may have been a confounding factor. Patients treated with FLAI-3 (16%), however, showed unsatisfactory outcomes (median OS 8.8 months, CR rate 29%) even when considering the unfavorable baseline characteristics of this subgroup. Despite the relatively high CR rate, most patients eventually relapsed, leading to an unsatisfactory long term DFS lower than 30%. However, the selected subgroup of patients who underwent allo-HSCT showed a 5-year DFS of 55% from transplant, confirming its important role for eligible patients. Finally, maintenance treatment showed some benefit in

retrospective series employing LDAC-based regimens(9) with an estimated 5-year OS of 36%. In summary, despite the limitations of its retrospective nature, our study represents one of the largest experience on the use of FLAI regimens in this age group. Importantly, FLAI was confirmed effective and safe in frailer patients after moderate dose reductions. Our findings should be considered when evaluating other emerging treatment options such as HMA and CPX-35. Moreover, FLAI may be evaluated in future studies also in association with target therapies (10).

## **Author contributions**

MC, EC, MVD, BB SD, EA, AC and DF treated the patients. MC, MVD collected data. MC wrote a draft of the manuscript. DF, EC, AC and BB revised the manuscript. MB supervised the research. All the authors reviewed the manuscript and approved it.

## **Conflict of interest**

The authors declare no conflict of interest.

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## **Legend to Figures**

**Figure 1.** Overall survival of the whole cohort

