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The FOSSIL Study: FLAG or standard 7 + 3 induction therapy in secondary acute myeloid leukemia

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ABSTRACT

Patients with secondary acute myeloid leukemia (sAML) have poor outcomes, with CR/CRi rates of 25–35% with standard 7 + 3 induction chemotherapy, while single center non-comparative analyses suggest promising outcomes with FLAG. We conducted a single-center, retrospective cohort study assessing outcomes in treatment-naïve patients with sAML treated with fludarabine, high-dose cytarabine, and granulocyte colony-stimulating factor (FLAG, n = 40) compared with 7 + 3 (n = 66). Median patient age was 63 years (range: 27–82) in the FLAG group and 60 years (range: 21–76) in the 7 + 3 group ($P = 0.968$). Patients treated with FLAG achieved higher overall response rates (CR + CRi + MLFS) compared to 7 + 3 (70% vs. 48%, $P = 0.043$). FLAG was well tolerated, with only one induction death (30-day mortality rate, 3% vs. 8%, $P = 0.405$) and no cases of cerebellar toxicity. Duration of neutropenia was significantly shorter with FLAG (median 16 vs. 23 days, $P < 0.001$). Half of the FLAG-treated patients proceeded to consolidative therapy compared with only 27% of those who received 7 + 3 ($P = 0.022$). Overall survival was comparable between groups (8.5 mos, FLAG *vs.* 9.1 mos, 7 + 3; $P = 0.798$). Thus, FLAG may represent a low-cost treatment strategy in sAML that produces higher response rates and promising survival outcomes with minimal treatment-related toxicity. Further studies are required to prospectively compare FLAG to the newly FDA-approved CPX-351 in sAML.

1. Introduction

Secondary acute myeloid leukemia (sAML) refers to a heterogeneous group of patients with AML arising from either an antecedent hematopoietic disorder (AHD) or prior treatment with chemotherapy and/or radiotherapy [1]. Outcomes in this subgroup of patients, which comprises approximately 25–30% of acute leukemias, are poor. Response rates to conventional chemotherapy are low (~25–35%), and patients frequently experience treatment-related morbidity and mortality (90-day mortality of ~25%) [2,3]. The poor prognosis is potentially explained by advanced age at diagnosis and a higher frequency of poor-risk cytogenetics [4]. Despite the dismal prognosis, progress in the area of sAML has been stagnant until recently, as the standard of care has remained the same as that for *de novo* AML and consists of an anthracycline plus cytarabine (7 + 3). Complete remission (CR) rates using 7 + 3 in sAML are unacceptably low (25–35%), thus clinical trial enrollment, novel approaches to treatment, and allogeneic hematopoietic cell transplant (alloHCT) when remissions are achieved remain important considerations for eligible patients [5]. CPX-351, a liposomal formulation of cytarabine and daunorubicin in a 5:1 molar ratio, represents a novel approach to the treatment of sAML FDA approved in 2017. A multi-center Phase III randomized controlled trial including

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only patients with sAML demonstrated an overall survival benefit with CPX-351 over 7 + 3 [5]. Aside from recent data including CPX-351, literature comparing various induction regimens in patients with sAML is limited at this time.

Although typically reserved for the salvage setting, high-dose cytarabine-based regimens offer an alternative approach to primary remission-induction therapy. Bashey, et al. reported on their experience using fludarabine, high-dose cytarabine, and granulocyte colony-stimulating factor (FLAG) in 24 patients with treatment-naïve AML. Importantly, 13 patients (54%) had secondary AML. FLAG resulted in complete remission and complete remission with incomplete hematologic recovery (CR, CR/CRi) rates of 58% and 75%, respectively, across the entire cohort [6]. Later, in 2010, Ferrara, et al. published their experience utilizing a modified FLAG regimen in 64 patients with AML arising from MDS. One cycle of FLAG induction resulted in a CR/CRi rate of 67%, and 79% of patients proceeded to consolidative therapy [7]. In Bashey, et al. and Ferrara, et al., deaths due to infectious complications prior to neutrophil recovery occurred in 12% and 14% of patients, respectively. Non-hematologic toxicities of grade 2 or greater were not reported in Bashey, et al. Grade 2 or greater non-hematologic toxicities in Ferrara, et al. were mostly hepatic in nature and consisted of increases in liver enzymes (8%) and serum bilirubin (5%) [6,7]. Löwenberg, et al. investigated the effects of daunorubicin dose intensification to 90 mg/m^2 compared to 45 mg/m^2 in older adults whose median age was 67. Thirty-day mortality rate was 11% in the dose-escalated cohort and 12% in the conventional dose cohort. Other toxicities included infectious complications, of which 76% were grade 3. Median duration of neutropenia was 26 days in both dose groups [8]. Given the poor response rates and tolerability of conventional 7 + 3 induction therapy, we compared response rates with FLAG induction versus standard 7 + 3 induction in patients with sAML.

2. Methods

In this single-center, retrospective cohort study, we screened the University of Michigan Health System (UMHS) Leukemia Database to identify adults over the age of 18 with treatment-naïve sAML who received either FLAG (fludarabine 30 mg/m^2/day (days 1–5), cytarabine 2 g/m^2/day (days 1–5), filgrastim 300–480 mcg/day (days 1-count recovery)) or standard 7 + 3 (daunorubicin 45–90 or idarubicin 10–12 mg/m^2 and cytarabine 100 mg/m^2) induction chemotherapy from November 2002 to September 2016 (Fig. 1). sAML was defined in accordance with World Health Organization 2008 guidelines as AML with an antecedent myelodysplastic syndrome (MDS) or myeloproliferative neoplasm (MPN) (MDS/MPN), or AML following cytotoxic chemotherapy [9]. Patients with acute promyelocytic leukemia (APL), relapsed or refractory AML, or those who received induction chemotherapy at an outside institution were excluded. Cytogenetic risk stratification was based on National Comprehensive Cancer Network (NCCN) guidelines, version 3.2017 [10]. Molecular mutation data, including FLT3-ITD, FLT3-TKD, NPM1, CEBPα, IDH1/2, were also collected.

Patients received a single cycle of FLAG or 7 + 3. Those failing to achieve a complete remission (CR), complete remission with incomplete hematologic recovery (CRi), or morphologic leukemia-free state (MLFS) proceeded to alternative re-induction strategies and were deemed induction failures for the purpose of this analysis. CR was defined as a blast percentage < 5% in the post-treatment bone marrow biopsy with count recovery as evidenced by an absolute neutrophil count greater than 1000 μL^{-1} and platelet count > 100,000 μL^{-}1 without transfusion [11]. Patients who met criteria for blast clearance with residual neutropenia (ANC < 1000 μL^{-1}) or thrombocytopenia (platelet count < 100,000 μL^{-}1) achieved a CRi. MLFS was defined as blast clearance without hematologic recovery. This study was approved by the institutional review board at the University of Michigan.

2.1. Study endpoints and statistical analyses

The primary outcome was overall response rate (ORR), reported as the combination of CR, CRi, and MLFS (CR + CRi + MLFS). Secondary endpoints included overall survival (OS), 30- and 60-day mortality, relapse-free survival (RFS), CR/CRi, duration of neutropenia, incidence of febrile neutropenia and bacteremia during induction, intensive care unit (ICU) admission during induction, ICU length of stay, and the proportion of patients able to proceed to consolidative therapy (consolidation chemotherapy or alloHCT). Overall survival was defined as the time period between the start of induction chemotherapy and the date of death, measured in months. Thirty- and 60-day mortality reflect the proportion of patients who died within 30 or 60 days of the start of induction. Relapse-free survival refers to the interval between the start of induction chemotherapy and date of relapse. All data were analyzed using SPSS software, version 24.0 (SPSS, Inc., Chicago, IL). Continuous, normally distributed variables were compared using a 2-tailed Student's *t*-test, and continuous, non-normally distributed variables were compared using the Mann-Whitney *U* test. Categorical variables were compared using Pearson's chi-square or Fisher's exact test, where appropriate. An alpha-level of 0.05 was considered statistically significant. A multivariate analysis for the primary outcome of ORR was performed to ensure that confounding variables did not impact response rate. Variables with an entry probability of < 0.2 on univariate analysis were included in the multivariate analysis. In the case of co-linear variables, only one variable was chosen. A time to event analysis (OS) was assessed via the Kaplan-Meier method and compared using the log-rank test. The Cox proportional hazards regression model was used to analyze the effect of induction regimen and other possible confounding variables on OS.

3. Results

A total of 106 patients were included in this study. Forty patients were treated with FLAG and 66 were treated with 7 + 3. Both groups were well matched in terms of baseline and disease characteristics, with the exception of more therapy-related AML patients in the FLAG group (48% FLAG *vs.* 20% 7 + 3, $P = 0.004$). AML arose after an AHD in 68% of FLAG patients and 83% of 7 + 3 patients ($P = 0.092$). Median patient age was 63 years in the FLAG group and 60 years in the 7 + 3 group ($P = 0.968$) (Table 1). Molecular characteristics were no different between the two groups. The ORR in the FLAG cohort was 70% (n = 28) compared to 48% (n = 32) in the 7 + 3 cohort ($P = 0.043$) (Table 2). Multivariate analysis revealed that baseline differences between groups did not impact response rate (Table 3). Median overall survival did not differ between groups and was 8.5 and 9.1 months with FLAG and 7 + 3, respectively ($P = 0.798$) (Fig. 2). In the multivariate Cox regression analysis, advanced age was associated with a decreased OS (Fig. 2). Among evaluable patients, 5-year OS was 22% (6/27) in the FLAG group and 6% (3/51) in the 7 + 3 group (p = .054).

More patients who received FLAG were able to proceed to consolidation with chemotherapy, alloHCT, or both (50% versus 27%, $P = 0.022$). Relapse-free survival was not significantly different between groups and was 4 months with FLAG and 5 months with 7 + 3 ($P = 0.101$). The rate of febrile neutropenia was 80% (n = 32) in the FLAG cohort and 91% (n = 60) in the 7 + 3 cohort ($P = 0.141$). Rates of bacteremia did not differ between groups at 38% with FLAG and 35% with 7 + 3 ($P = 0.836$). Intensive care unit (ICU) admission during induction was nearly doubled, although not statistically different, in those who received 7 + 3 as compared to FLAG (26% versus 15%) ($P = 0.231$). There were no cases of cerebellar toxicity in patients receiving FLAG treatment. There were five deaths within the first month of induction in the 7 + 3 group compared to one death with FLAG ($P = 0.405$). Median time to ANC recovery was statistically significantly different at 16 days in the FLAG cohort and 23 days in the 7 + 3 cohort ($P < 0.001$). Table 2 summarizes response rates, while