

Randomized multicenter phase II study of flavopiridol (alvocidib), cytarabine, and mitoxantrone (FLAM) versus cytarabine/daunorubicin (7+3) in newly diagnosed acute myeloid leukemia

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Manuscript received on February 16, 2015. Manuscript accepted on May 21, 2015.

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Supplemental Data

Methods:

Patient Eligibility:

Inclusion Criteria:

- Adults ≥ 18 years and ≤ 70 years with pathologic confirmation of newly diagnosed AML ($\geq 20\%$ bone marrow blasts)
- Newly diagnosed AML, subtypes M0,1,2,4-7 but excluding M3 (APL), including those with the following poor risk features
 - Antecedent hematologic disorder including myelodysplasia (MDS)-related AML (MDS/AML) and prior myeloproliferative disorder (MPD)
 - treatment-related myeloid neoplasms (t-AML/t-MDS)
 - myeloid sarcoma, myeloid proliferations related to Down Syndrome, and blastic plasmacytoid dendritic cell neoplasm
 - AML with multilineage dysplasia (AML-MLD)
 - adverse cytogenetics¹
- Patients who have received hydroxyurea alone or have received non-cytotoxic therapies previously for MDS or MPN (e.g., thalidomide or lenidomide, interferon, cytokines, 5-azacytidine or decitabine, histone deacetylase inhibitors, low-dose cytoxan, tyrosine kinase or dual TK/src inhibitors) were eligible.
- ECOG performance status 0-3, patients ≥ 65 years of age must have ECOG performance status ≤ 2 prior to developing leukemic symptoms.
- Patient must be able to give informed consent
- Renal function: Serum creatinine ≤ 2.0

- Hepatic enzymes (ALT, AST) ≤ 5 x upper limit of normal unless leukemic infiltration
- Total bilirubin ≤ 2.0 mg/dl unless Gilbert's Disease, hemolysis or leukemia
- Left ventricular ejection fraction $\geq 45\%$

Exclusion Criteria:

- Any previous treatment with flavopiridol
- Concomitant chemotherapy, radiation therapy, or immunotherapy
- Hyperleukocytosis with $\geq 50,000$ blasts/uL. Leukopheresis or hydroxyurea may be used immediately prior to study drug administration for cytoreduction. Must be stopped 24 hours before first dose of study chemotherapy.
- CBF AMLs associated with t(8;21) or M4eo subtype (inv[16] or t[16;16]), as diagnosed by morphologic criteria, flow cytometric characteristics, and rapid cytogenetics or FISH or molecular testing.
- Acute Progranulocytic Leukemia (APL, M3)
- Active CNS leukemia
- Active, uncontrolled infection. Patients with infection under active treatment and controlled with antibiotics were eligible.
- Active, uncontrolled graft vs. host disease (GVHD) following allogeneic transplant for non-AML condition (e.g. MDS, lymphoid malignancy, aplastic anemia). Patients with GVHD controlled on stable doses of immunosuppressants were eligible.
- Presence of other life-threatening illness
- Patients with mental deficits and/or psychiatric history that preclude them from

giving informed consent or from following protocol

- Pregnant and nursing patients were excluded.

Treatment:

Patients were randomized by REDCap², a centralized computer-generated allocation procedure, 2:1 to receive FLAM (arm A): flavopiridol 50 mg/m² IV days 1-3, cytarabine 2 gm/m² CI IV days 6-8 (667 mg/m²/day), and mitoxantrone 40 mg/m² IV day 9 or 7+3 (arm B): cytarabine 100 mg/m²/day CI IV days 1-7, and daunorubicin 90 mg/m² IV days 1-3 (idarubicin 12 mg/m² IV days 1-3 was substituted as needed for lack of daunorubicin availability). Patients were stratified according to the following risk factors: 1) Age \geq 50 years, 2) Secondary AML (defined as treatment-related AML or AML from antecedent hematologic disorder) and/or known adverse cytogenetics,¹ and 3) Hyperleukocytosis (white blood cell count \geq 50,000/mm³). Neither participants nor investigators were masked to treatment allocation.

All patients received a BM biopsy on day 14 unless medically contraindicated. Residual leukemia on day 14 was defined as BM blasts \geq 5% morphologically with overall cellularity \geq 10%. Arm B patients were eligible to receive an additional cycle of induction therapy, 5+2 (cytarabine 100 mg/m²/day CI IV days 1-5, daunorubicin 45 mg/m² IV days 1-2) in the setting of residual leukemia on day 14. Post-induction treatment was performed according to physician preference. Arm A patients were eligible to receive 1 additional cycle of consolidation therapy with FLAM or 1-4 cycles of IV cytarabine 1.5-3 gm/m² IV Q12hours for 6 doses (HiDAC) upon CR. Patients on arm B were eligible to receive 1-4 cycles of HiDAC upon CR. Patients who achieved CR and

had a suitable donor were eligible for a myeloablative or nonmyeloablative allogeneic stem cell transplant (SCT) after induction or consolidation therapy.

Supportive care:

All patients received prophylaxis against tumor lysis syndrome (TLS) with allopurinol and a phosphate binder 24 hours prior to chemotherapy through day 8 of therapy. Rasburicase was used to treat TLS per institutional policy. Prompt treatment with IV dexamethasone was performed for any patient with evidence of cytokine release syndrome. All patients received antibiotic prophylaxis against gram negative gastrointestinal infections, candidiasis, and herpes simplex virus. To prevent cytarabine-related conjunctivitis, all patients received corticosteroid eye drops day 1 prior to initiation of cytarabine and continued for at least 7 days. Use of colony stimulating factors was not permitted.

Response and toxicity:

BM aspirates and biopsies were performed before treatment, on day 14 of treatment, and at hematologic recovery or when leukemia regrowth was suspected. Hematologic recovery was defined as absolute neutrophil count (ANC) $\geq 1,000/\text{mm}^3$ and transfusion-independent platelet count $\geq 100,000/\text{mm}^3$. Response criteria were defined according to standard definitions.¹ Adverse events were graded by NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

Statistical analysis:

The study was designed to compare CR rates between FLAM and 1 cycle of 7+3, using a Bayesian approach for interim monitoring for futility. The primary analysis would conclude a significant benefit for FLAM if the one-sided p value from a Fisher's exact test <0.10 . A sample size of 165 patients, randomized 2:1 to FLAM or 7+3, respectively, yielded 85% power to detect an increase in the probability of CR from 55% with 7+3³⁻⁵ to 75% with FLAM. In addition to the planned primary endpoint analysis, we also analyzed CR rates between FLAM and 7+3+/-5+2 by Fisher's exact test with a one-sided p value, analogous to the primary endpoint analysis. Interim monitoring for futility and toxicity, based on the probability of a statistically significant treatment difference if the study continued, was initiated after 45 patients received treatment and after each subsequent group of 30 patients were treated. Logistic regression was used to model CR as a function of treatment group and the randomization stratification factors (i.e., age ≥ 50 years, secondary AML and/or known adverse cytogenetics, and hyperleukocytosis).

Secondary endpoints included toxicity comparisons, overall survival (OS), and event-free survival (EFS). OS was defined from date of randomization to death or last known follow-up. EFS was defined as date of randomization to the first occurrence of persistent AML after 1 cycle of induction, relapse or death. Patients were censored for EFS if they had received non-protocol therapy or a SCT. Time to full hematologic recovery was defined for patients who achieved CR as the date of CR to date of recovery. All significance tests for secondary endpoints were two-sided with a significance p value <0.05 . To explore heterogeneity of treatment effects between various subgroups, logistic

regression models with terms for treatment, the patient subgroup, and their interaction were fit. P values were derived from likelihood ratio tests and are considered exploratory. OS, EFS, and time to hematologic recovery probabilities were calculated using the Kaplan-Meier method and tested for differences between treatment arms with the log-rank test. Survival data was analyzed as of January 23, 2015. Analyses were completed with R version 3.1.1.⁶ Statistical analysis was performed by ALB and GLR. All authors had access to the primary clinical trial data.

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