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Research paper

# Report of the relapsed/refractory cohort of SWOG S0919: A phase 2 study of idarubicin and cytarabine in combination with pravastatin for acute myelogenous leukemia (AML)

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ABSTRACT

Inhibition of cholesterol synthesis and uptake sensitizes acute myeloid leukemia (AML) blasts to chemotherapy. A Phase 2 study of high dose pravastatin given in combination with idarubicin and cytarabine demonstrated an impressive response rate [75% complete remission (CR), CR with incomplete count recovery (CRi)]. However, this population was a favorable risk group as eligible patients had to have a CR/CRi lasting ≥3 months following their most recent chemotherapy. Therefore, the study was amended to treat patients with poor risk disease including those with CR/CRi < 6 months following their last induction regimen or with refractory disease. Here, we present results in this poor risk group. This trial included a significant number of patients with poor risk cytogenetics (43%) and poor risk molecular mutations. The response rate was 30% and approximately one-fourth of patients were able to proceed to allogeneic hematopoietic stem cell transplant (HSCT). The median overall survival for patients proceeding to allogeneic HSCT is 27.1 months. Although this trial did not meet criteria for a positive study based on the response rate ($p = .062$), these results are encouraging given the poor risk population and suggest that targeting the cholesterol pathway may have therapeutic benefit in AML.

## 1. Introduction

The treatment of relapsed/refractory acute myeloid leukemia (AML) remains challenging and novel therapies are needed. AML blasts frequently overexpress the genes for the LDL receptor and 3-hydroxy-3-methylglutaryl coenzyme reductase (HMG-CoAR) and therefore import and synthesize cholesterol at higher levels than normal myeloid progenitors [1]. Patients with AML and high white blood cell counts sometimes have marked hypocholesteremia at the time of diagnosis suggesting increased cholesterol metabolism and this typically resolves when patients achieve a complete remission (CR) [1,2]. These observations suggest that AML cells may require high levels of cholesterol for their survival and that abnormalities in cholesterol homeostasis are necessary for AML cell survival [2]. In addition, inhibition of cholesterol synthesis and uptake sensitizes AML blasts to chemotherapy [2]. Thus, targeting the cholesterol pathway represents a potential therapeutic approach.

A previous Phase 1 trial demonstrated encouraging results with high dose pravastatin in combination with IA (idarubicin and intermediate dose cytarabine) [1]. This led to a Phase 2 trial of this combination in patients with relapsed AML [3]. The response rates in this trial were impressive: 75% CR/CR with incomplete count recovery (CRi). However, this population was a favorable risk group as eligible patients had to have a CR/CRi lasting ≥3 months following their most recent chemotherapy. Therefore, this study was amended to treat patients with poor risk AML (CR/CRi < 6 months following their last induction regimen or refractory disease). Here, we report the results in this poor risk group.

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## 2. Methods

Patients were treated at SWOG institutions from April 2013 through November 2014. The protocol (registry: ClinicalTrials.gov Identifier: NCT00840177) was approved by each institution's review board and signed informed consent was obtained from all registered patients. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Pravastatin was supplied by Bristol Meyers Squibb (New Brunswick, NJ, USA). Eligibility included: age ≥18 years, relapsed/refractory AML, cardiac ejection fraction ≥45%, CR/CRi following the most recent chemotherapy < 6 months, and no prior hematopoietic stem cell transplant (HSCT). Patients receiving 1 induction course with 7 + 3 (cytarabine + anthracyline) and a day 14 bone marrow with ≥5% blasts were eligible. Treatment consisted of pravastatin (1280 mg by mouth on Days 1–8), idarubicin 12 mg/m$^2$/day intravenous (IV) days 4–6, and cytarabine 1.5 g/m$^2$/day continuous IV infusion days 4–7. Patients achieving a CR could also receive 2 cycles of consolidation with oral pravastatin 1280 mg by mouth days 1–6, idarubicin 12 mg/m$^2$/day IV days 4–5, and cytarabine 1.5 g/m$^2$/day continuous IV infusion days 4–5. CR and CRi were defined by International Working Group (IWG) criteria [4]. Toxicity was graded and defined according to CTCAE version 3.0 for routine toxicity reporting and according to version 4.0 for serious adverse event reporting. The attribution of toxicities was decided by the treating physician.

### 2.1. Statistics

Thirty-seven patients were to be accrued. If ≥12 patients achieved CR or CRi, the regimen would be considered sufficiently effective (critical level of 5% if the true CR rate is 20%) and power of 87% (if the true CR rate is 40%). These numbers are based on a stratification system described by Estey et al. [5]. Study data were analyzed by Hongli Li, M.S. and Megan Othus, Ph.D., leukemia committee biostatisticians at the SWOG Statistical Center (Seattle, WA). All authors had access to primary clinical trial data.

## 3. Results

Patient characteristics are listed in Table 1. Forty-six patients with a median age of 57 years (range 23–75) were enrolled. Twenty-four patients (52%) were male and the median white blood count (WBC) was 2600/uL (range 200–450,000). The median time from diagnosis to registration was 4.3 months (range 0.7–49.5). At the time of registration, 65% of patients were primary refractory and 35% had relapsed. The number of prior treatment regimens included: 1 (46% of patients), 2 (37% of patients), 3 (7% of patients), and 4 (11% of patients). Prior salvage therapy included: 7 + 3 (cytarabine plus an anthracycline), single agent clofarabine, high dose cytarabine, MEC (mitoxantrone, etoposide, cytarabine), aurora kinase inhibitor (AMG-900), FLAG (fludarabine, high dose cytarabine, granulocyte colony stimulating factor) ± anthracycline (idarubicin), 5-azacitidine, and CLAG (cladribine, high dose cytarabine, granulocyte colony stimulating factor) ± anthracycline (mitoxantrone). Forty-two percent of patients were considered to have either treatment-related AML (n = 4; 9%) or had a prior history of myelodysplastic syndrome (n = 15; 33%). Cytogenetic risk defined by NCCN criteria [6]: 43% poor, 52% intermediate, and 4% missing. Molecular mutation data was not required at study entry. However, most sites collected this data. The frequency of various mutations included: FLT3 [7/36 patients: 6 internal tandem duplications (ITD), 1 tyrosine kinase domain (TKD)], NPM1 (3/33 patients), c-kit (1/4 patients), WT1 (0/3 patients), CEBPalpha (3/31 patients with single mutations); IDH1 (4/23 patients); IDH2 (2/23 patients), JAK2 (0/3 patients), DNMT3A (4/24 patients), p53 (1/3 patients), ras (3/5 patients), and RUNX1 (1/2 patients). Table 2 outlines Grade 3–5 treatment-related toxicities. No myositis or unexpected toxicities were observed. Fig. 1 outlines the distribution of patients with respect to subsequent transplant and consolidation therapy after salvage therapy on trial. One evaluable patient received 1 cycle of consolidation therapy on protocol. Eleven patients were able to proceed to transplant (10 with allogeneic HSCT and one with NK transplant).

The response rate was 30% CR/CRi (95% CI: 17.7%, 45.8%). The p-value comparing 30%–20% (the null response rate) is 0.062 at a one-

**Table 1**
Patient Characteristics (n = 46).

| | |
|---|---|
| Median Age | 57 years (range 23–75) |
| Gender | |
| Male | 52% (n = 24) |
| Female | 48% (n = 22) |
| Median time from initial diagnosis to registration | 4.3 months (range 0.7–49.5) |
| Disease status | |
| Primary refractory | 65% |
| Relapse | 35% |
| Median WBC at registration | 2600/uL (range 200–450,000) |
| Cytogenetic risk by NCCN criteria | |
| Poor | 43% |
| Intermediate | 52% |
| Missing | 4% |

**Table 2**
Treatment-related toxicities (Grade 3–5).

| | Grade 3 | Grade 4 | Grade 5 |
|---|---|---|---|
| **Hematologic** | | | |
| Hemoglobin | 15 | 6 | 0 |
| Leukocytes | 0 | 17 | 0 |
| Lymphopenia | 2 | 7 | 0 |
| Neutropenia | 1 | 15 | 0 |
| Platelets | 1 | 17 | 0 |
| **Non-hematologic** | | | |
| Transaminase | 3 | 0 | 0 |
| Alkaline phosphatase | 1 | 0 | 0 |
| Infectious colitis | 1 | 0 | 0 |
| Creatinine | 1 | 0 | 0 |
| Diffuse capacity of the lung for carbon monoxide (DLCO) | 0 | 0 | 1 |
| Diarrhea | 8 | 0 | 0 |
| Dyspnea | 1 | 0 | 0 |
| Fatigue | 2 | 0 | 0 |
| Febrile neutropenia | 26 | 5 | 0 |
| Gastrointestinal infection | 1 | 0 | 0 |
| Gastrointestinal pain | 4 | 0 | 0 |
| Genitourinary Infection | 1 | 0 | 0 |
| Hypoalbuminemia | 6 | 0 | 0 |
| Hypocalcemia | 1 | 1 | 0 |
| Hypokalemia | 3 | 0 | 0 |
| Hyponatremia | 1 | 0 | 0 |
| Hypophosphatemia | 2 | 0 | 0 |
| Hypotension | 0 | 0 | 1 |
| Hypoxia | 3 | 0 | 0 |
| Bacteremia | 1 | 8 | 2 |
| Lung, hemorrhage | 1 | 1 | 0 |
| Lung infection | 7 | 1 | 0 |
| Mucositis | 2 | 1 | 0 |
| Muscle pain | 2 | 0 | 0 |
| Nausea | 3 | 0 | 0 |
| Neurologic infection | 0 | 1 | 0 |
| Opportunistic infection | 2 | 0 | 0 |
| Rash | 1 | 0 | 0 |
| Renal failure | 0 | 1 | 0 |
| Typhlitis | 1 | 0 | 0 |
| Ulceration | 1 | 0 | 0 |
| Weight Loss | 2 | 0 | 0 |

n = 46; the numbers are below are the numbers of patients with the specified grade toxicities during protocol treatment.