# Induction of Acute Myeloid Leukemia with Idarubicin, Cytarabine and Cladribine

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**Abstract.** *Background: Daunorubicin and cytarabine has been the standard-of-care for induction therapy for acute myeloid leukemia (AML). Adding cladribine to daunorubicin (60 mg/m$^2$) and cytarabine has increased complete remission (CR) rates and median overall survival (OS). However, the efficacy of adding cladribine to 7+3 with other anthracyclines is unknown. Patients and Methods: We retrospectively evaluated patients with AML receiving induction with idarubicin, cytarabine and cladribine (ICC) between 1/1/2010 and 06/30/2015 at the Methodist University Hospital in Memphis, Tennessee. Institutional Review Board approval was obtained for the study. Patient, disease characteristics and outcomes were analyzed with GraphPad Prism, Microsoft Excel and SPSSv19.0 software. Results: Twenty-four patients induced with ICC for AML were identified. Thirteen (54.2%) had at least one high-risk feature. Hypoplastic marrow was achieved in all by day 14; 19 (79.2%) achieved CR. Thirty-day mortality was 8.3%; 33-month OS and disease-free survival were 56% and 36%, respectively. Conclusion: Induction of AML with ICC was associated with a high CR rate and OS in our high-risk population.*

The first step in the successful treatment of acute myeloid leukemia (AML) is to achieve complete remission (CR) with an acceptable early mortality rate (1). Three days of daunorubicin and seven days of cytarabine (7+3) has remained the standard induction therapy for AML for nearly three decades despite 20-40% of patients failing to achieve CR (2-4).

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Optimizing this standard regimen with various alterations has shown improved results. Fernandez *et al*. reported an improved CR rate and duration of overall survival (OS) in young adults with AML treated with a higher dose of daunorubicin (90 mg/m$^2$) compared to the standard dose (45 mg/m$^2$). This benefit was seen in patients with favorable or intermediate-risk cytogenetics and not in patients older than 50 years or with unfavorable-risk cytogenetic profiles (5). Lowenberg *et al*. showed more rapid and higher response rates with the higher dose of daunorubicin in patients older than 60 years with AML compared to the conventional dose. There was no significant difference in OS between the two groups. However, the sub-group analysis showed that patients in the age group of 60-65 years, the youngest age group in the study, benefited the most from the escalated dose (CR of 73% *vs*. 51% and 2-year OS of 38% *vs*. 23%). Patients with favorable-risk cytogenetics had a 2 year OS of 60% compared to 19% for patients with unfavorable-risk cytogenetics with the escalated dose (6).

Substituting idarubicin for daunorubicin in the 7+3 regimen has also led to superior results. Higher rates of CR with idarubicin as compared to daunorubicin, with a similar toxicity profile, were demonstrated by Wiernik *et al*. (7). Even when compared to high-dose daunorubicin (80 mg/m$^2$), idarubicin (12 mg/m$^2$) has led to marginally better long-term outcomes in patients over 50 years with AML. Gardin *et al*. reported a median OS of 20.8 months in patients 50-59 years old, 14.2 months in 60-69 years old and 12.2 months in patients over 70 years old (8). As such, Mandelli *et al*. suggested replacing daunorubicin with idarubicin for AML in patients not receiving an allogeneic stem cell transplant (9).

The use of cladribine, a deoxyadenosine analog, in addition to daunorubicin and cytarabine has shown promise. Martin *et al*. suggested cladribine-based regimens to be explored in both first-line and salvage settings. Their study reported a complete response of 53% in patients given cladribine-based regimens as induction chemotherapy and 44% in patients given salvage chemotherapy. The regimens were well-tolerated and had minimal extramedullary toxicity (10).The Polish Adult Leukemia Group (PALG) added cladribine to

7+3 using a lower dose of daunorubicin (60 mg/m$^2$) and reported increased CR rates and OS in patients under 60 years old. Although not powered to search for differences in specific sub-groups, the OS was markedly improved in patients with an initial white blood cell count greater than $50\times10^9$/l, that is considered high risk factor. Improved results were also seen in patients with unfavorable karyotypes (11).

The potential benefit of the addition of cladribine to 7+3 with other anthracyclines, as well as optimal anthracycline dose, is unknown. Our study evaluated the addition of cladribine to full-dose idarubicin and cytarabine as the induction regimen in an older and high-risk AML population.

## Patients and Methods

This retrospective study was approved by the Institutional Review Board at the Methodist University Hospital (MUH) in Memphis, TN, USA. All patients who received in-patient idarubicin, cytarabine and cladribine (ICC) therapy between January 2010 and June 2015 at MUH were identified through electronic medical records. MUH is the major academic campus and principal teaching hospital of the University of Tennessee and caters to the urban, predominantly African American Memphis population. The patients' charts were reviewed and data were extracted by two of the authors (EW and OJ), with a third author (MGM) resolving any discrepancies. The patients who were 18 years of age and older were eligible if they received ICC for untreated AML. Dosing consisted of idarubicin (12 mg/m$^2$) on days 1-3, cytarabine (100-200 mg/m$^2$ at the discretion of the treating medical oncologist) on days 1-7 and cladribine (5 mg/m$^2$) on days 1-5. The variables studied were age at diagnosis, gender, race, history of myelodysplastic syndrome (MDS) or myeloproliferative neoplasm (MPN), cytogenetics, Internal tandem duplications of fms-related tyrosine kinase 3 (*FLT3-ITD*) and nucleoplosmin gene (*NPM1*) mutation status and outcome [30-day mortality, CR, OS and disease free survival (DFS)].

In accordance with the National Cancer Institute Working Group criteria, CR was defined as <5% bone marrow blasts with >1,000/l neutrophils and >100,000/l platelets; complete remission with incomplete platelet recovery was defined with the same bone marrow and neutrophil criteria but without platelets >100,000/l. The responses were defined based on morphology alone and not on cytogenetic or molecular studies (12).

The primary end-point of the study was the CR rate. Secondary endpoints were OS, DFS and 30-day mortality. The survival times were calculated from the first day of chemotherapy until death or the date of the last follow-up. Data were tabulated and analyzed using Microsoft Excel (Microsoft 2010; Redmond, Washington, USA) and GraphPad Prism version 6.00 (for Windows; GraphPad Software, La Jolla, CA, USA). Continuous variables were analyzed as means and categorical variables were analyzed as percentages. OS and DFS were determined by Kaplan–Meier estimates.

## Results

Twenty-four patients with AML underwent induction with ICC. The median age at diagnosis was 58 (range=24-68) years. Thirteen patients (54.2%) were Black and 11 (45.8%) were White. There were 16 males (66.7%) and eight females (33.3%).

Evaluation of our patient population revealed that 13 patients (54.2%) had at least one high-risk feature. High-risk features were defined by age greater than 60 years, high-risk cytogenetics, prior treatment with cytotoxic chemotherapy, FLT3 expression, or antecedent hematological disorder. Two patients (8.3%) had favorable cytogenetics, 15 patients (62.5%) had intermediate-risk cytogentics, and four (16.7%) had poor-risk cytogenetics. Results were not available for three patients. Patient and disease characteristics are summarized in Table I.

Hypoplastic bone marrow was achieved in all patients by day 14 and 19 (79.2%) achieved CR based on day 30 bone marrow examination. Thirty-day mortality was 8.3% (two patients). One patient died from typhlitis and the other died secondary to complications from pulmonary leukostasis which was present upon presentation prior to initiation of induction chemotherapy. Thirty-three month OS was 56% (Figure 1) and DFS was 36% (Figure 2).

## Discussion

The combination of cladribine with anthracyclines and cytarabine as induction therapy for AML has shown promising results (13-15). Juliusson *et al*. showed a CR rate of 51% and 24 month OS of more than 30% with one course of 5 mg/m$^2$ cladribine given before intermediate dose cytarabine 1 g/m$^2$ for 2 h *bid* for 4 days with idarubicin at 10 mg/m$^2$/day for 2 days (16). The Polish Adult Leukemia Group looked at the efficacy of cladribine as an addition to the standard 7+3 chemotherapy regimen in patients under 60 years old. Their protocol consisted of daunorubicin at 60 mg/m$^2$/day on days 1-3, cytarabine at 200 mg/m$^2$/day on days 1-7 and cladribine at 5 mg/m$^2$ in 2-hour infusions on days 1-5 (DAC). They showed a CR rate of 64% after one course of DAC and a 3-year OS of 45% (11).

As far as we are aware, our study is the first to evaluate the addition of cladribine to 7+3 using full-dose idarubicin. Our population consisted of older patients, with the median age at diagnosis being 58 years (range=24-68 years). The PALG showed promising results with cladribine in a young population with the median age being 48 years (range=18-60 years). Hahn *et al*. reported age as a poor prognostic factor in AML either due to worsening performance status or increased incidence of unfavorable cytogenetics with increasing age (1). Appelbaum *et al*. also showed a higher early mortality rate, lower CR rate and a lower chance of higher OS with increasing age in patients with AML (17). More than 50% of our patients were African American. Literature has shown that the African American race is associated with a poor outcome in AML irrespective of insurance status and access to healthcare. Previous studies looking at newer induction regimens for AML only had a 15% representation of the African American population in their study population (1, 18-20). We treated a high-risk

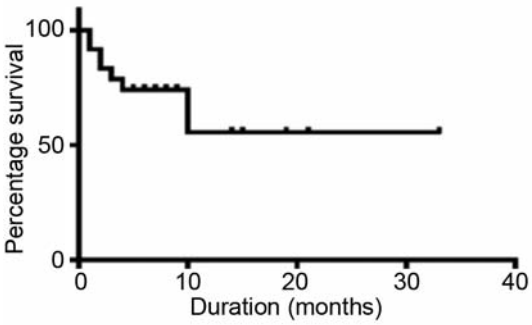


Figure 1. *Overall survival for the entire study population.*

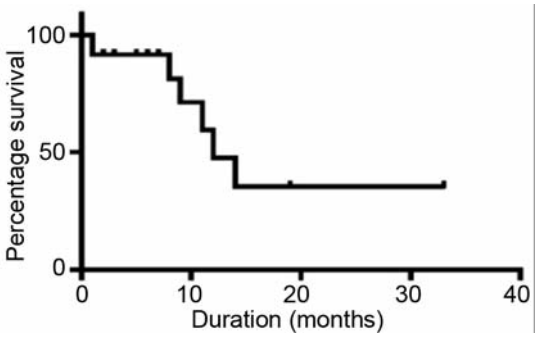


Figure 2. *Disease-free survival for the entire study population.*

population based on the aforementioned high-risk features present in our patients (21, 22). Thirteen (54.2%) patients had at least one high-risk feature and four (16.7%) patients had overall poor cytogenetics. Only two patients (8.3%) had favorable cytogenetics. The PALG study had 8% patients with favorable, 53% with intermediate and 16% with unfavorable cytogenetics.

Our CR rate of 79.2% is higher than previously reported studies using cladribine with anthracyclines and cytarabine. We also found a high 33-month OS of 56%. Our 30-day mortality was 8.3% which was comparable to the 11% shown by the PALG with DAC, suggesting that ICC was effective without increasing mortality, despite treating a higher risk population. Previous studies by Fernandez *et al*. (5), Lowenberg *et al*. (6), Patel *et al*. (23) and Nazha *et al*. (4), which aimed at optimizing induction regimens either by dose escalation or drug addition, have shown promising results in a patient population that is not considered high risk with regards to age, race or cytogenetics.

Idarubicin has been associated with better long-term outcomes when compared to daunorubicin in elderly patients (cure rates of 16.6% with idarubicin *vs*. 9.8% with daunorubicin). Factors contributing to this include the effect of idarubicin on AML cells expressing various drug resistance phenotypes, prolonged half-life of its metabolite and better cellular uptake of the drug (8, 24).

Antibody-directed chemotherapy is another novel approach as induction chemotherapy. Gemtuzumab ozogamicin (GO), a humanized antibody against CD33, at a dose of 3 mg/m$^2$ has been shown to reduce relapse risk and improve overall survival, with little increase in toxicity (3). This drug was initially approved in 2000 for relapsed as well as newly-diagnosed AML. In 2010, after a randomized study by the Southwest Oncology Group showed excessive toxicity with no improved efficacy, GO was voluntarily withdrawn from the market. Since then, several randomized studies have shown acceptable toxicity along with better efficacy with GO, making a case for it to be re-approved (25).

Table I. *Patient and disease characteristics (n=24).*

| Median (range) age, years=58 (24-68) | |
|---|---|
| Characteristic | No. of patients (%) |
| Male/female | 16 (66.7%)/8 (33.3%) |
| White/Black | 11 (45.8%)/13 (54.2%) |
| History of MDS | 5 (20.8%) |
| Cytogenetics | |
| Favorable | 2 (8.3%) |
| Intermediate | 15 (62.5%) |
| Poor | 4 (16.7%) |
| Unknown | 3 (12.5%) |
| FLT3-positive* | 2 (8.3%) |
| NPM1-positive** | 3 (12.5%) |

MDS: Myelodysplastic syndrome; FLT3: fms-related tyrosine kinase 3; NPM1: nucleoplosmin. *Isolated occurrence in intermediate-risk cytogenetics; **isolated occurrence in intermediate-risk cytogenetics.

Despite many advances in treating AML, prognosis still remains poor. Optimizing induction therapy to achieve higher CR rates is pivotal for better long-term survival.

Several limitations exist in this study. The design was retrospective and the patient population was small. This was also a single-arm study with no direct comparison in patient outcomes to those treated with the standard 7+3 induction regimen. Although our regimen of ICC was used in a small population, it showed encouraging results in an older and high-risk population. Larger prospective trials are required to confirm the efficacy of this regimen.

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