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Efficacy and Toxicity of Induction Therapy with Cladribine, Idarubicin, and Cytarabine (IAC) for Acute Myeloid Leukemia

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Abstract. *We report our single-center experience with cytarabine and idarubicin for induction therapy for acute myeloid leukemia (AML) with an additional 5 days of cladribine (IAC therapy). From July 2012 to September 2014, 38 patients completed a full course of IAC induction. Median patient age was 61 years, 61% of patients were ≥60 years old, and 71% were male. The complete remission (CR) rate was 63% following a single induction course, three patients (8%) required a second induction course to achieve CR, for an overall response rate of 71%. The median duration of severe neutropenia was 30.5 days. Thirty-two percent of patients developed mucositis, 76% experienced diarrhea, and 61% developed a rash. Incidence of CR following IAC induction therapy for AML was comparable to historical data, but with frequent diarrhea, rash, and fungal infections. This study found IAC efficacy and toxicity was similar irrespective of age.*

Among adults (>18 years old) who develop acute myeloid leukemia (AML), induction therapy will result in complete remission (CR) in 60-70%, and about half of these will survive for 3 years or more. However, these numbers do not reflect the complexity added by age, co-morbidity and disease risk classification (1). Importantly, survival is less common and shorter in patients over 60 years of age, for reasons which have not been completely delineated, but likely due in part to the higher proportion of such cases with poor genetic risk features (2). It is significant to note that the median age for AML diagnosis is 66 years, and therefore that the majority of people stricken with AML are older (3).

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Therapy for AML has been slow to evolve. For over 40 years, standard therapy has included 7 days of cytarabine and 3 days of anthracycline ('7+3' regimen) (4). Other combinations have been studied in an effort to improve outcomes in older persons, without overwhelming success. However, the Polish Adult Leukemia Group (PALG) reported that adding cladribine to daunorubicin-containing 7+3 regimen (so called '7+3+5' or DAC) increased the complete remission (CR) rate, reduced hospital stay, and did not significantly increase toxicity in a study population of patients younger than 60 years (5, 6). The authors concluded that cladribine increases the potency of the 7+3 regimen, and may improve long-term survival in patients between 40 and 60 year old. National Comprehensive Cancer Network (NCCN) guidelines have recently included DAC as an option for AML induction therapy, albeit in patients under 60 years old (7).

At Saint Louis University Hospital (SLU), DAC has been modified to use idarubicin (IAC) as the preferred anthracycline (8, 9). Two retrospective reviews found substitution of daunorubicin by idarubicin in combination with cladribine and cytarabine was safe and effective (10, 11). In contrast with the PALG studies (5, 6), SLU routinely utilizes IAC induction in patients over 60 years of age. Here we report the SLU experience with IAC regarding response and toxicity and analyze outcomes as a function of age.

Patients and Methods

Study design. This was a retrospective study examining AML and high-risk myelodysplasia (*i.e.* blast count >10%) in patients diagnosed and treated between 7/1/12 and 9/30/14 at SLU Hospital. This study received approval from the SLU Institutional Review Board and SLU Hospital Research Compliance Committee (IRB # 25011).

Study population. Eligible patients were 18 years or older and had received at least one full cycle of IAC (12 mg/m^2 idarubicin ×3 days, 200 mg/m^2 cytarabine ×7 days, and 5 mg/m^2 cladribine ×5 days). Patients had a diagnosis of AML or high-risk myelodysplasia, and excluded those who: had acute promyelocytic leukemia; were pregnant; had impaired renal (creatinine clearance <50 ml/min),

hepatic (total bilirubin >2.5 mg/dl), or cardiac (left ventricular ejection fraction <50%) function.

Study outcomes. Primary outcome assessed was response (CR rate) after one or two courses of IAC. Secondary outcome was toxicity, including duration of neutropenia, incidence of mucositis, diarrhea, rash, infections and intensive care unit admissions.

Data collection. The SLU hospital electronic health record (EHR) (EPIC Systems, Verona WI) was searched for patients treated between 7/1/2012 and 9/30/2014 using the International Classification of Diseases ninth revision codes 205.00 (AML) and 208.9 (unspecified leukemia). In cases that preceded the EHR resource, paper charts were manually extracted to identify appropriate patients. Collected data included: baseline serum chemistry and complete blood count values; molecular prognostic indicators (genetic mutations); cytogenetics (karyotype and fluorescent *in situ* hybridization) data; and blast percentage in peripheral blood and bone marrow. Fourteen-day post-induction and CR bone marrow cytomorphology, flow cytometry; and genetic marker perseverance were recorded.

Regarding adverse events, clinical notes were searched for the terms "diarrhea", "rash", and "mucositis". Additionally, the medication administration record was interrogated to find therapies specific for mucositis or diarrhea, while microbiological and pathological data were assessed for positive culture and skin biopsy data.

CR was defined per World Health Organization classification with <5% blasts in bone marrow, absolute neutrophil count (ANC) >1000 cells/mm^3, platelet count >50,000 cells/mm^3, and hemoglobin >8 g/dl, with transfusion independence for >1 week (12). Duration of severe neutropenia was defined as the time from the start of therapy to ANC >500 cells/mm^3 (13). Duration of neutropenia was defined as the time from the start of therapy until ANC >1000 cells/mm^3 (13).

Statistical methods. Outcomes are reported *via* descriptive statistics. Subgroup analysis of remission rate and toxicities stratified by age was conducted using the chi-squared test. A *p*-value of less than 0.05 was considered significant. IBM SPSS Statistics Version 22.0.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis.

Results

Patient and disease characteristics. Thirty-eight patients met the inclusion criteria, out of a total of 48 cases identified. Ten patients were excluded due to abbreviated treatment, non-diagnosis (<10% blasts), and therapy outside of the study window. Two out of 38 patients had refractory anemia with excess blasts and one had chronic myelomonocytic leukemia. The patient group was skewed towards male sex (71%) and older age (median=61 years; range=20-78 years; mean=57.5±13.7 years) than that treated by the PALG. Median white blood cell count, marrow blast percentage, cytogenetics and NCCN leukemia risk classification are summarized in Table I. Three patients were classified as having high-risk myelodysplasia (blast count between 10-19%), and one patient did not have sufficient data for NCCN leukemia risk stratification (7).

Response rate. Outcomes are summarized in Table II. Twenty-seven out of 38 patients (71%) achieved a CR, 63% requiring only a single induction course of induction therapy. Another three patients had incomplete CR for an overall response of CR + CRi of 79%. When stratified by leukemia risk, 7/8 (88%) patients with favorable risk had an overall response, compared to 13/14 (93%) with intermediate risk. Only 10/16 (63%) with unfavorable risk had a response (p=0.10). Fifteen of 38 patients (39.5%) were <60 years old, of which 87% (13/15) had an overall response. In comparison, overall response was achieved 17/23 (74%) of patients ≥60 years of age, p=0.35.

Toxicity. Myelosuppression: All patients experienced neutropenia and thrombocytopenia. As shown in Table II, two different neutropenia states were followed in the 33 patients surviving to hospital discharge. ANC >500 cell/mm^2 is regarded as severely neutropenic with high risk of gram-negative rod infection from gut mucosa. A second ANC threshold of 1,000 cells/mm^2 reflects the productivity of a fully recovering marrow.

Rash: During induction therapy, 23/38 patients (61%) developed skin rash; the average time to first rash (mean±SD) was 10.2±4.2 days. Eight cases were biopsied: one was attributed to trauma, two to hypersensitivity, one to Sweet's syndrome, two to perivascular dermatitis, one to chemotherapy-induced rash, and one to psoriaform dermatitis (Table III).

Gastrointestinal symptoms: Twelve patients (32%) experienced mucositis, with symptom duration ranging from 2-48 days. Out of the 29 patients experiencing diarrhea, 13 (45%) of these suffered longer than 7 days. The average number of days of loperamide administration was 3.6 ± 0.8 days (median=2 days). Sixteen percent of patients became infected with *Clostridium difficile*, with 20.8% occurrence in those aged 60 years or more *versus* 7.1% in the younger population (p=0.264) (Table III).

Mucositis: Mucositis was documented in 32% of patients, with median duration of 11.5 days. Patients received diphenhydramine, aluminum, magnesium, simethicone, viscous lidocaine-containing mouth rinse for a mean of 4.7±1.9 days.

Infections: Thirty-seven out of 38 patients (97%) had at least one bout of fever during their hospitalization. Infections were bacteria implicated in 53%, while five patients (13%) had fungal infections. Two patients had both bacteria and fungus isolated (Table III). Most common infection was found on blood culture, followed by pneumonia and *Clostridium difficile* gastrointestinal infection (Table III). Five patients developed vancomycin-resistant enterococcus, in each case cultured from the bloodstream. *Stenotrophomonas* was twice isolated from the blood and once from the lungs from a bronchial alveolar lavage. *Escherichia coli* accounted for two cases of bacteremia and one of pneumonia. The three fungal

Table I. *Patient characteristics, n=38.*

Patient characteristics	n	%	Median	Range
Age, years	-	-	61	20-78
Male gender	27	71	-	-
Molecular markers				
FLT3 ITD	5	13	-	-
FLT3 TKD	1	3	-	-
NPM1	8	21	-	-
CEBPA	1	3	-	-
Cytogenetics				
Favorable	4	11	-	-
Intermediate	21	55	-	-
Unfavorable	12	32	-	-
Not assessed	1	3	-	-
NCCN leukemia risk				
Favorable	8	21	-	-
Intermediate	14	37	-	-
Poor	16	42	-	-
Hematological parameters				
WBC, $\times 10^3/mm^3$	-	-	15.3	1.0-220.2
Hemoglobin, g/dl	-	-	8.4	5.0-13.5
Platelets, $\times 10^3/mm^3$	-	-	52.5	6-681
ANC, cells$\times 10^3/mm^3$	-	-	1	5-20.5
Peripheral blood blasts	-	-	28	0-95
Bone marrow blasts, %	-	-	52	12-99
Bone marrow cellularity, %	-	-	90	60-100

ANC: Absolute neutrophil count; *CEBPA*: CCAAT/Enhancer binding protein alpha; *FLT3*: fms like tyrosine kinase 3; ITD: internal tandem duplication; TKD: tyrosine kinase domain; *NPM1*: nucleophosmin1; NCCN: National Comprehensive Cancer Network.

Table II. *Hematological recovery and remission outcomes.*

Outcome measure	n	%	Median	Range
CR				
CR first induction	24	63	-	-
CR second induction	3	8	-	-
Overall CR	27	71	-	-
CRi	3	8	-	-
Response rate (CR+CRi)	30	79	-	-
CR by age				
<60 Years	12/15	80*	-	-
≥60 Years	15/23	65	-	-
CR by NCCN leukemia risk				
Favorable	7/8	88*	-	-
Intermediate	11/14	79	-	-
Poor	9/16	56	-	-
Hematological recovery n=(33)§				
Days to ANC >500/mm^3	-	-	30.5	21-75
Days to ANC >1000/mm^3	-	-	35	22-78
Hospitalization days	-	-	33	24-98

ANC: Absolute neutrophil count; CR: Complete response; CRi: incomplete CR; NCCN: National Comprehensive Cancer Network. *One patient lost to follow-up, not considered to be CR. §Of patients who survived to hospital discharge.

Table III. *Toxicities and adverse events, n=38.*

Toxicity/adverse event	n	%	Median	Range
Mucositis	12	32	-	-
Diarrhea	29	76	-	-
Rash	23	61	-	-
Neutropenic fever	37	97	-	-
ICU admission	11	29	-	-
Documented infection	22	58	-	-
Clostridium difficile infection	6	16	-	-
Bacterial infection	20	53	-	-
Fungal infection	5	13	-	-
Death within 28 days	4	11	-	-
Survival to hospital discharge	33	87	-	-
Patients with diarrhea				
Days of diarrhea	-	-	8	1-33
Days of loperamide	-	-	2	0-15
Patients with mucositis				
Days of mucositis	-	-	11.5	2-48
Days of mouthwash	-	-	2	0-21

ICU: Intensive care unit.

pneumonia cases had the following isolates: *Candida dubliniensis*, *C. tropicalis*, and Zygomycetes. There was one instance of craniofacial aspergillosis and one of bloodstream infection with *C. krusei*.

Hospitalization, intensive care, and mortality. This study focused on initial hospitalization outcomes only. The median length of hospitalization was 33 days (range=24-98 days). Twenty-nine percent of patients required intensive care unit (ICU) admission. Five patients (13.2%) did not survive to hospital discharge and of these, four died within 28 days, for a treatment-related mortality rate of 11%. Four out of the five deaths during induction therapy were of patients aged 60 years or older (p=0.34). All five patients died with an element of respiratory failure precipitated by cardiac failure at day 15; *Stenotrophomonas* bacteremia and sepsis at day 20; cirrhosis, encephalopathy and fluid overload at day 21; stroke, sepsis and pneumonia day at 21; *Candida tropicalis* pneumonia and sepsis at day 32, respectively.

Discussion

Data from prospective clinical trials show that 60-70% of patients with AML aged 50 years or less and 50% of those over 50 years old achieve CR with induction therapy (7). By comparison, IAC at SLU (CR of 71%, median age=61 years) was found to be similar in efficacy to historical data, comparing favorably with the PALG DAC studies (median ages 45 and 47 years, respectively) (5, 6), and similar to recent reports at other institutions using IAC [median age 58

years and 43 years] (10, 11). However, our study is different from others as our population was older, with 23 patients aged 60 years or more; notably this population was excluded by the PALG and Shen *et al*. (5, 6, 10). Consequentially, this retrospective report provides unique information regarding toxicity and induction outcomes in older patients with AML receiving IAC.

Importantly, age stratification did not show differences in efficacy or toxicity in patients 60 years of age or older in this study, despite typically poorer historical CR rates in that group compared to younger patients (7). The CR rate of 65% among patients 60 years and older in our study is comparable to that reported by Juliusson *et al*. in which they treated patients over the age of 60 years with intermittent cladribine, intermediate-dose cytarabine (1 g/m^2) twice per day for 4 days and 2 days of idarubicin 10 mg/m^2 (14). In our hands, IAC did not confer significant CR advantage for patients with poor cytogenetic classification (45.5% *vs*. 82.6% with intermediate and 75% with favorable, p=0.08) nor when stratified by NCCN leukemia risk (56% *vs*. 79% with intermediate and 88% with favorable, p=0.208). In contrast, the 2012 PALG study reported a trend towards overall survival advantage as well as reduced mortality in patients with unfavorable cytogenetics (6). Shen *et al*. also showed that IAC was as effective (CR=77.8 *vs*. 63%) and tolerable as idarubicin and cytarabine (10). In another retrospective study, 24 patients received IAC (some with lower dose cytarabine) and 79.2% achieved a CR within 30 days, and 33-month overall survival of 56% and 36% disease-free survival was recorded (11).

SLU patient recovery from severe neutropenia (ANC >500 cells/mm^3) was a median of 30.5 days compared to PALG data with DAC, which was a median of 23 (5) and 24 days (6). Shen *et al*. used lower dose IAC regimen and recorded shorter median time to ANC recovery at 20 days (10).

Skin rash during induction therapy for AML often occurs, but is infrequently described in the literature. We recorded 62% (23/38) of cases developing skin complaints. Often, the rash was attributed to chemotherapy and was not biopsied. Thirty-five percent (8/23) of rashes were biopsied, with one only attributed to chemotherapy. Rash is expected with cytarabine-containing regimens, and in IAC, cladribine may potentiate development of hypersensitivity *via* a proposed mechanism of lymphopenia and T-cell imbalance (15).

Two studies inform our expectations of gastrointestinal toxicity with 7+3 induction therapy for AML. Peric *et al*. found that 41.7-50% of patients developed generalized oral and gastrointestinal mucositis (16), while Camera *et al*. revealed that 42% developed diarrhea during induction (17). We observed oral mucositis in 32% (12/38) and diarrhea in 76% (29/38) of patients. Our incidence of diarrhea was high, and may have been a result of the additive gastrointestinal toxicity of cladribine and cytarabine, or may represent an overestimate due to our search strategy.

Atallah and colleagues reviewed 1,534 adults with AML to establish expected baseline toxicities with standard induction therapy (18). They showed an overall incidence of documented infection was 64%. The SLU overall documented bacterial infection rate (53%) was similar to those seen in PALG studies [37% (5) and 49% (6)]. The PALG infection rates did not significantly differ between the 7+3 and the DAC arms in either study (5, 6). However, we recorded 13% of patients (5/38) as having fungal infections compared to 8% incidence in the PALG study (5).

There are several limitations to this study that should be noted. Because we report a retrospective analysis of the initial induction of 38 patients at a single institution, this study has limited power in ascertaining the performance of the IAC regimen, especially in specific patient subgroups. It is important to note that while not statistically significant, there was a higher incidence of death and *C. difficile* infections noted in the older patient population. Larger trials may have more power to detect differences in outcomes and adverse events. Additionally, our rates of adverse events, such as rash, mucositis and diarrhea, only reflect toxicities that became clinically significant. This may lead to under-reporting of toxicities as minor events which may not have been detected or documented in the medical record.

Conclusion

This report is unique due to the detailed review of toxicities associated with IAC and the older age group of patients. Additionally, SLU uses higher doses of idarubicin and cytarabine in combination with cladribine compared to other published studies (10, 11). Several caveats limit the interpretation of this study, namely it is a single-arm, retrospective chart review with a limited number of patients. However, we do show an encouraging CR rate comparable to prior studies, and no significant differences in remission or incidence of toxicities in patients with AML aged 60 years or more. Cladribine has been implicated in driving increased cytarabine uptake to enhance the potency of this regimen; however, this mechanism may also increase toxicity. Direct comparison of CR, overall survival, and toxicity events after IAC *versus* standard 7+3 regimen in older patients would be informative on this issue, especially as part of a prospective randomized trial. For now, however, IAC may be appropriate for AML treatment in selected older patients.

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