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Research Article

Outcomes of Intermediate Dose Cytarabine Re-Induction Following Traditional Induction Chemotherapy in Acute Myeloid Leukemia

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Abstract

Introduction: Up to 40% of acute myeloid leukemia (AML) patients do not achieve remission with initial induction chemotherapy and require re-induction, for which there is no accepted standard.[1-5] Current literature describes varying percentages of patients who achieve complete response (CR) or complete response with incomplete hematologic recovery (CRi) based on re-induction strategy, with CR or CR/CRi rates ranging from 28% to 78%.[12-15] This study assessed outcomes for AML patients with residual disease post initial intensive therapy who received intermediate dose cytarabine (IDAC) re-induction.

Methods: This study is a single center retrospective analysis of 62 adult patients who received IDAC re-induction for AML between December 1st, 2014, to September 30th, 2022.

Results: Thirty-two (52%) patients achieved the primary outcome of CR or CRi, with 26 (42%) patients who achieved CR and 6 (10%) who achieved CRi. Overall survival at one-year was 65% (n=40).

Conclusion: The CR rate seen with IDAC re-induction was comparable to other cytarabine alone strategies and fell within the reported ranges for combination regimens. Overall, these results support IDAC for re-induction as an acceptable and well tolerated strategy in AML treatment.

Keywords: Acute myeloid leukemia; Intensive induction chemotherapy; Intermediate dose cytarabine; Induction failure, re-induction

Introduction

Acute myeloid leukemia (AML) is the most common acute leukemia in adults and accounts for 80% of all acute leukemia cases.[1] Cytarabine at various doses is frequently used in both the initial and subsequent treatment of AML. Cytarabine dose intensity can be classified as standard dose (SDC, 100-200 mg/m^2), intermediate dose (IDAC, 1,000-2,000 mg/m^2), and high dose (HiDAC, 2,000-3,000 mg/m^2). In addition to different dosing strategies, the number of doses can vary based on both setting and reference used.

SDC is commonly utilized in the induction regimen 7+3, which is a continuous infusion of cytarabine for seven days in combination with an anthracycline for three days. Despite recent advances leading to more patients achieving complete response (CR) with induction therapy, 20-40% of patients will require re-induction [1]. It was previously thought that patients in the induction setting receiving SDC may develop resistance to lower doses of cytarabine [2,3]. As this concern for resistance has been explored over the years, there has not been data to support the development of cross-resistance or that using higher doses of cytarabine as a salvage agent following previous cytarabine lessens efficacy [2,3]. Therefore, in the setting of re-induction, a regimen of single agent cytarabine using higher doses than used in initial induction is common. Historically, HiDAC was more frequently chosen, but IDAC has gained popularity as it has been shown to have similar outcomes to HiDAC but with decreased toxicity [3,4].

Recent updates to both the European LeukemiaNet (ELN) and the National Comprehensive Cancer Network (NCCN) guidelines support the use of IDAC, among other strategies, in AML re-induction. Our decision to re-induce based on interim bone marrow biopsy follows general guidance, including most recent guidelines. Re-induction was standard with residual blasts of > 20% and considered on a case-by-case basis in more ambiguous scenarios. The ELN guideline dosing is 1000-1500 mg/m^2 intravenous (IV) over 3 hours every 12 hours on days 1-3. The NCCN guideline dosing is 1000-1500 mg/m^2 IV over 3 hours every 12 hours for 4-6 doses for 1-2 cycles [2,5]. The University of Kansas Health System commonly uses IDAC re-induction in patients who received intensive initial induction therapy with 7 + 3. Specifically, for patients ≥ 60 years old, IDAC 1000 mg/m^2 IV over 3 hours every 12 hours on days 1-3 is the recommended dosing [2,4-7]. For patients < 60 years old, IDAC 1500 mg/ m^2 IV over 3 hours every 12 hours on days 1-3 is preferred.

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Despite recommendation for use of IDAC by these two prominent guideline organizations, there is currently no formally accepted standard [2,5,8,9]. This lack of guidance surrounding re-induction regimens and their associated outcomes allows for significant ambiguity. Some common re-induction regimens recommended by the 2022 ELN guidelines, include additional anthracycline plus SDC, liposomal daunorubicin/cytarabine (CPX-351), or HiDAC [5]. The 2023 NCCN re-induction recommendations include additional anthracycline plus SDC, CPX-351, or HiDAC [2]. Other strategies may include mitoxantrone, etoposide, and cytarabine (MEC), cladribine, cytarabine, mitoxantrone, and filgrastim (CLAG-M), or fludarabine, cytarabine, and filgrastim with or without idarubicin (FLAG ± Ida). This ambiguity stems from the limited data existing in the re-induction setting and contrasts with the larger body of literature available in the primary refractory, induction failure, or salvage setting [10]. The lack of data specific to re-induction is partially due to a history of inconsistencies in definitions. There has been deliberation on the number of cycles and intensity of said cycles that should occur in the induction setting prior to a patient being considered primary refractory versus having induction failure [11]. More recently, acceptance of a consistent classification of failing at least two intensive cycles before labeling disease as primary refractory or having induction failure has occurred. This allows a second cycle of induction also known as re-induction to be utilized for patients [5]. A review of current literature describes varying percentages of patients achieving response in the re-induction setting, with CR or CR/CRi rates ranging from 28% to 78%. These results include 56% for cytarabine alone, 43% to 59% for 7 + 3, and 28% to 78% for FLAG [11-15]. Of the existing data in this setting, it is primarily composed of single-center, retrospective studies. These studies lack data regarding leukemia characteristics, in large part due to recent advances in AML diagnostics. Given the lack of prospective randomized data comparing these re-induction strategies, we analyzed AML patients treated with IDAC re-induction at our institution. The purpose of this study is to evaluate the safety and efficacy of this institution's re-induction regimen IDAC in AML patients who previously received 7 + 3 ± midostaurin or gemtuzumab ozogamicin (GO) for intensive initial induction.

The primary objective of this study is to determine the rate of complete response (CR) and complete response with incomplete hematologic recovery (CRi) for AML patients who received IDAC re-induction in comparison to other re-induction strategies based on previously published literature. Secondary outcomes include overall survival (OS) at one year and infection rate.

Methods

Study Design

This study was a single center retrospective analysis performed at the University of Kansas Medical Center. Patients were identified via a report generated by the electronic medical record. Patients were assessed from December 1, 2014 through the time of data analysis on September 30, 2022. Patient information included demographics, AML classification, pertinent genetic and molecular data, induction regimen, re-induction regimen characteristics, pre- and post-induction bone marrow biopsy results, blood cell counts, and antimicrobial use throughout re-induction therapy. The study protocol was approved by the University of Kansas Medical Center Institutional Review Board.

Inclusion/Exclusion Criteria

Patients included in the study were 18 years of age or older and received IDAC re-induction after receipt of a 7 + 3 based chemotherapy regimen. The decision to re-induce was based on the day 14 (or day 21 in midostaurin-containing regimens) bone marrow biopsy and followed NCCN guidance. Patients who received IDAC for AML consolidation or in the setting of relapse, as well as Philadelphia chromosome positive, bi-phenotypic, and chronic myeloid leukemia blast crisis were excluded.

Outcomes

The primary outcome of this study was the rate of CR/CRi after re-induction IDAC. Per NCCN guidelines, CR was defined as myeloid blasts less than 5% in the post first induction bone marrow, absolute neutrophil count (ANC) > 1,000 k/uL and platelets ≥ 100,000 k/uL, and transfusion independence. Reported ANC and platelets are those at time of post re-induction bone marrow biopsy. White blood cell (WBC) count was reported if no ANC was available due to severe leukopenia. Transfusion independence was defined as no transfusions from time of post re-induction bone marrow biopsy for 8 weeks. CRi was defined as all CR criteria and transfusion independence, but with persistent neutropenia (ANC < 1,000 k/uL) or thrombocytopenia (< 100,000 k/uL) [3]. Patients were considered as non-evaluable for response if lacking an assessment of adequate bone marrow response. The non-evaluable criteria includes individuals that experienced early death, withdrawal prior to response assessment, or a suboptimal bone marrow precluding assessment based on ELN guidelines [5]. Secondary outcomes included overall survival at one year and infection rate. Infection rate was assessed as any treatment for documented bacterial, fungal, or viral infections (excluding prophylaxis) initiated or escalated from previous treatment after the initiation of IDAC until post-IDAC bone marrow biopsy.

Statistical Analysis

Statistical analysis was performed using IMB SPSS Statistics, Version 28.0. All continuous variables are represented as a mean ± standard deviation [SD] for parametric data and median ± interquartile range [IQR] for non-parametric data. For parametric data, continuous variables were evaluated using a student t-test and all categorical variables were evaluated using a chi squared test. For non-parametric data all categorical variables were evaluated using a chi-square or Fisher's Exact test.

Results

Patient Population

Sixty-three patients who received IDAC re-induction were identified. A total of 62 patients met criteria and were included in the analysis. The only patient excluded was based on failure to receive full re-induction course. The mean age was 55.7 years (STD ± 12.8 years) and mean BSA was 2.05 m^2 (STD ± 0.3 m^2). Thirty-seven (60%) patients were male and 56 (92%) were Caucasian. Thirty-two (52%) patients were classified as adverse risk, 27 (43%) were intermediate risk, and 3 (5%) were favorable risk per 2022 European LeukemiaNet (ELN) criteria. Of the 62 patients, 13 (21%) had monocytic differentiation,

two (3%) had a TP53 mutation, and 16 (26%) had FLT3 mutations. Of those with FLT3 mutations 12 (75%) were ITD positive and 5 (31%) were TKD positive, with one patient having both mutations. The most common initial induction regimen was 7 + 3, with 50 (81%) patients, followed by 11 (18%) 7 + 3 with midostaurin, and 1 (2%) 7 + 3 with GO. This institution utilizes 7 + 3 with midostaurin in those with FLT3 mutated AML and 7 + 3 with GO in core binding factor (CBF) AML who are considered fit. The number of patients who received each induction regimen can be found in Table 1. Of note, not all patients who were FLT3 mutation positive received midostaurin, given that part of the study period was prior to midostaurin approval. Additionally, the most common induction daunorubicin dose was 90 mg/m^2 in 37 patients (61%), followed by 60 mg/m^2 in 23 patients (34%), and 45 mg/m^2 in 1 patient (2%). Of note, one patient received daunorubicin at an outside facility and the dose was not able to be identified; the patient who received 45 mg/m^2 was appropriately reduced due to hepatic impairment. Forty-six (74%) patients received a cytarabine dose of 1500 mg/m^2 compared to 16 patients (26%) who received a dose of 1000 mg/m^2. The reduced dose of 1000 mg/m^2 was appropriate for these patients given age > 60 at time of re-induction. Post first induction bone marrow blasts were > 50% in 34 (55%), 20% to 50% in 23 (37%), and < 20% in 5 (8%) of patients. Most patients requiring IDAC reinduction were based on day 14 or day 21 marrow results showing residual disease (n=42, 75%), while a minority of patients had required reinduction IDAC based on residual disease on recovery bone marrow biopsy (n=14, 25%). All other baseline clinical characteristics are described in Table 1.

Table 1: Clinical Characteristics.

Characteristics	N = 62
Initial Induction Regimen, n (%) 7 + 3 7 + 3 with midostaurin 7 + 3 with GO	 50 (81) 11 (18) 1 (2)
Daunorubicin Dosing (mg/m^2), n (%)* 90 60 45	 37 (61) 23 (38) 1 (2)
Re-induction Cytarabine Dosing (mg/m^2), n (%) 1500 1000	 46 (74) 16 (26)
Post First Induction Bone Marrow Blasts (%), n (%)	
> 50	34 (55)
20-50	23 (37)
< 20	5 (8)
ANC at Time of Post Re-Induction Bone Marrow (k/uL), mean (STD)	3.4 (3.6)
WBC if no ANC Available (k/uL), mean (STD)	6.4 (7)
Platelets at Time of Post Re-Induction Bone Marrow (k/uL), mean (STD)	254 (201)
Time to Count Recovery (days), mean (STD)*	25 (7)

*Value is less than total population due to missing information or not meeting the criteria of the assessed data point,
7 + 3: standard dose cytarabine continuous infusion for seven days with an anthracycline for three days,
GO: Gemtuzumab Ozogamicin; ANC: Absolute Neutrophil Count; WBC: White Blood Cell.

Table 2: Efficacy.

Characteristics	N = 62
Responders, n (%) CR/CRi	 32 (52)
CR CRi	26 (42) 6 (10)
Non-Responders, n (%) Non-Evaluable, n (%) Survival at One Year, n (%)	24 (39) 6 (10) 40 (65)

CR: Complete Response; CRi: Complete Response with incomplete hematologic recovery.

Table 3: Safety.

Characteristics	N = 56
Febrile Neutropenia, n (%)	32 (52)
Fungal Infection, n (%) No Probable Proven	 47 (92) 4 (6) 1 (2)
Antimicrobials at Start of Re-Induction, n (%)	40 (65)
Advance in Antimicrobials During Re-Induction, n (%)	39 (63)
Proceeded to Transplant, n (%)	32 (53)
Death at Time of Chart Review, n (%)	31 (51)
Time from Re-Induction to Death (months), mean (STD)	9 (9.3)

Efficacy

Of the 62 patients who received IDAC re-induction, 32 (52%) achieved CR (n=26, 81%) or CRi (n=6, 19%). Of note, in determining transfusion independence as a factor for CR versus CRi, patients may have received consolidation or additional chemotherapy impacting this variable. The remaining 30 patients include 24 non-responders and 6 considered non-evaluable for response. Non-evaluable for response to IDAC includes patients who decided to not pursue additional treatment transferring to home or hospice (n=3) and those who expired prior to the ability to assess response (n=3). Of the 57 patients who were evaluable for response, a CR rate of 56% was seen. Of the 32 patients with post first induction bone marrow blasts > 50% who were evaluable for response, 19 (59%) had a CR/CRi. For all patients who received re-induction, 40 (65%) patients were still alive at one year.

CR/CRi versus no CR/CRi

Patients who achieved CR or CRi were compared to those who did not achieve CR or CRi. Results are shown in Table 4. Patients who achieved CR or CRi had statistically significant higher blood counts. Risk category was unable to be assessed statistically. When evaluating risk category numerically, there were slightly more adverse risk patients who did not respond, while more intermediate and favorable patients achieved a response. Additionally, time from re-induction to death was longer in patients who achieved CR or CRi, but not statistically significant (12 months versus 4.7 months; p=0.07). A subgroup analysis of patients with monocytic differentiation (n=12; p=0.93) or FLT3 mutations (n=15; p=0.73) did not differ significantly between response groups. Both patients with TP53 mutations did not achieve CR or CRi, this subgroup could not be assessed statistically. Higher bone marrow blast count at time of IDAC re-induction (p=0.64) or IDAC dosing (p=0.78) did not alter likelihood of CR/CRi. In addition, timing of re-induction did not show a significant difference between patients who received re-induction based off day 14 bone marrow biopsy versus those who were re-induced based off count recovery bone marrow (p=0.21).

Safety

At the start of the re-induction period, 40 patients (65%) were on antimicrobial treatment, escalated from prophylaxis. Throughout the re-induction period, 32 patients (52%) experienced febrile neutropenia. Thirty-nine patients (63%) required an escalation in their antimicrobials, either from prophylaxis to treatment or if currently on treatment expanded organism coverage. Patients were assessed for fungal infections based on the 2021 European Organization for the

Table 4: CR/CRi versus no CR/Cri.

Characteristics N = 56	CR/CRi n = 32	No CR/CRi n = 24	P-value
Age, n (%)			
> 60	12 (37.5)	13 (54)	0.21
≤ 60	20 (62.5)	11 (46)	
Sex, n (%)			
Female	19 (59)	14 (58)	0.94
Male	13 (41)	10 (42)	
BSA, mean (STD)	2.1 (0.3)	2.0 (0.3)	0.14
Risk Category, n (%)†			
Adverse	12 (38)	15 (62.5)	
Intermediate	17 (53)	9 (37.5)	N/A
Favorable	3 (9)	0 (0)	
Initial Induction Regimen, n (%)*			
7 + 3	26 (84)	18 (75)	0.49
7 + 3 with midostaurin	5 (16)	6 (25)	
Daunorubicin Dosing (mg/m^2), n (%)*			
90	22 (69)	12 (52)	0.26
60	10 (31)	11 (48)	
Cytarabine Dosing (mg/m^2), n (%)*			
1500	25 (78)	18 (75)	0.78
1000	7 (22)	4 (25)	
Post First Induction Bone Marrow Blasts (%), n (%)			
> 50	18 (56)	14 (58)	
20-50	12 (38)	7 (29)	0.64
< 20	2 (6)	3 (13)	
Time Between Bone Marrows (days), mean (STD)*	47 (11)	47 (17)	0.93
ANC at Time of Post Re-Induction Bone Marrow (k/uL), mean (STD)*	4.5 (4)	2.2 (2.8)	0.01
WBC if no ANC Available (k/uL), mean (STD)	9 (6.9)	0.3 (0.2)	0.01
Platelets at Time of Post Re-Induction Bone Marrow (k/uL), mean (STD)*	346 (206)	136 (118)	0.01
Time to Count Recovery (days), mean (STD)*	25 (6.4)	27 (9.8)	0.93
Timing of Post First Induction Bone Marrow			
Day 14 or 21	26 (81)	16 (67)	0.21
Count Recovery	6 (19)	8 (33)	

*Value is less than total population due to missing information or not meeting the criteria of the assessed data point,
†Contains a group of n = 0 that could not be assessed statistically,
ANC: Absolute Neutrophil Count; WBC: White Blood Cell.

Research and Treatment of Cancer/Mycoses Study Group Education and Research Consortium (EORTC/MSGERC) recommendations. Fifty-seven patients (92%) did not have a fungal infection, 4 (6%) had a probable fungal infection, and 1 (2%) had a proven fungal infection. Thirty-two (53%) of patients proceeded to allogeneic stem cell transplant. It was not assessed whether additional treatment was required prior to transplant or not. At time of study completion, 30 patients (49%) had died, with a median time from re-induction to death of 9 months. Of the 17 patients where cause of death could be identified, death was attributed to cardiogenic shock/arrest (n=6, 35%), progressive disease (n=5, 29%), respiratory failure (n=4, 24%), intracranial bleed (n=1, 6%), and pericarditis (n=1, 6%). The three individuals who were not evaluable for response based on death prior to meeting the response time point, expired between 10-12 days post re-induction. These deaths were not able to be attributed to disease. The causes of death in this group included cardiogenic shock/arrest (n=2) and respiratory failure (n=1).

Discussion

In this retrospective study, we measured the rates of CR/CRi to re-induction IDAC in patients who received a 7 + 3 based regimen as initial induction. For patients requiring re-induction following 7 + 3 with or without midostaurin or GO, IDAC re-induction led to a CR/CRi rate of 52% and a CR rate of 42%. There was no difference in whether patients achieved CR or CRi based on blast count prior to IDAC re-induction. Remarkably, patients with > 50% blasts after first induction had a 56% CR/CRi rate with IDAC re-induction. Unsurprisingly, those who did respond were seen to have higher neutrophil and platelet counts. Neutrophils and platelets at time of post re-induction bone marrow were the only statistically significant points seen in the CR/CRi versus no CR/CRi subgroup analysis. IDAC re-induction showed a response regardless of age, risk category, and common mutations. Additionally, IDAC dosing did not alter patient response, but age-based dosing is a potential confounding factor. Based on these findings, a specific population subset in which IDAC re-induction is preferred could not be identified, although the sample sizes for this subgroup analysis was small.

AML re-induction is a complex landscape with limited data and varying definitions. This ambiguity is an issue recognized and described well in AML literature [10,11]. Much of the existing data for patients who require additional therapy post induction lies within the primary refractory, induction failure, or salvage settings; many studies combine these patient populations into a single analysis. In the most recent ELN guidelines, the definition of refractory disease is defined as after two courses of intensive induction treatment or a defined landmark [5]. This aligns with the most widely accepted standard of two intensive induction cycles being required, but also proves the lack of uniformity by allowing other defined landmarks to be used. This non-uniformity is further exemplified as practitioners attempt to determine and identify what factors may be associated with worse outcomes or associated therapies by creating more complex definitions. An example of this can be seen from Ferguson et al. where refractory definitions exist for patients who do not respond after first induction as well as re-induction [16]. Another example of where definitions may differ includes in the setting of intensity, specifically with cytarabine, where some consider failure after two courses of SDC or just one course of HiDAC [17]. These evolving definitions along with mixed study populations in the post first induction setting complicate data interpretation and hinder applicability of existing literature to our population.

Despite the perplexity of definitions, our institution accepts that a second intensive induction in those who fail initial intensive induction should be utilized, although we lack consistent and conclusive information regarding the ideal regimen in this setting. In a review of the current literature, a re-induction CR and or CR/CRi range of 18% to 78% can be seen [12-15]. When this literature is assessed by re-induction strategy, a CR of 56% is seen for regimens containing cytarabine alone although at varying dosing strategies. While the specific number of patients that received an intermediate dose of cytarabine is not provided, our CR rate is similar to that reported by Fu et al [12]. When assessing other strategies, the repeat use of 7 + 3 or transition to FLAG had CR rates of 43% to 59% and 28%

to 78% respectively [13-15]. The wide range observed, even within the same re-induction strategy used, proves the vast study variability. Some of this variability can be seen in the initial induction and re-induction regimens. The many strategies available involve different doses of various chemotherapy combinations, which may or may not be equivalent. Additionally, the intensity of induction attempts can differ with potential differences in resistance and response when a second intensive regimen is used versus a less intensive therapy, though these differences are not consistent enough to be able to draw relevant conclusions.

Despite the growing body of evidence reporting favorable CR rates with single agent cytarabine, other centers continue to use alternatives such as HiDAC, FLAG-Ida, CLAG-M, and MEC. Since these regimens include higher doses of cytarabine and multiple agents in combination, they can be associated with higher toxicities. When examining HiDAC, where much of the previous literature assessed its place in the relapsed/refractory setting, alone versus in combination with additional chemotherapy agents such as anthracyclines or etoposide. While the added agents often led to higher CR rates, these were not statistically significant. Additionally, a study performed by Karanes et al. cited higher grade 3 toxicities, especially mucositis, and higher rates of consolidation dropout and mortality. This increase in toxicity seen was not present in all similar literature assessed and may have a different profile based on the chemotherapy agent used [18-20]. Even when our initial induction standard of 7 + 3 was used in the re-induction setting and compared against less intensive regimens, an increase in febrile neutropenia, transfusions, and length of hospitalization was seen [21]. While it is recommended that a second intensive cycle should be utilized, we need to understand the true intensity and tolerability in this high-risk patient population. Our study supported both efficacy and safety with utilization of IDAC in the re-induction setting.

This retrospective analysis provides valuable insight into the outcomes and safety profile in AML patients who received IDAC re-induction. The CR rate found in this study was similar to those seen with cytarabine alone strategies, and within range of those reported for 7 + 3 and FLAG, showing that IDAC for re-induction led to comparable CR rates as in other recommended re-induction strategies. When assessing current literature related to other re-induction strategies, direct comparison is challenging given different demographics, study designs, comparator arms, and outcomes assessed. Generalizing CR rates from an expansive body of literature leads to omission of key inter-study variability that could alter the basis of re-induction decisions. Our safety endpoints supported the importance of practices including antimicrobial prophylaxis, as well as vigilant monitoring and quick action to minimize infectious complications to help optimize these patients' outcomes.

Limitations of this study include the small sample size, leukemia heterogeneity, and single center, retrospective nature. It should also be noted that direct comparison of this study to the reported literature on other re-induction strategies cannot be done due to the retrospective nature. Additionally, multiple changes in clinical practice occurred throughout the data collection period that could not specifically be accounted for. Since the study period began, there is decreased turnaround time of fluorescence in situ hybridization (FISH) and next-generation sequencing (NGS), leading to quicker identification of a patients' risk category and targetable mutations. With the recent 2022 ELN guideline updates there was an expansion of risk criteria further delineating patient prognosis based off NGS. The addition of various mutations to the adverse risk category has led to an increased number of patients being defined as adverse risk on presentation. This contrasts with previous versions of the guidelines where criteria were less stringent. Additionally, quicker access to mutational status and new drug approvals has led to a changing therapeutic landscape. The quick identification of a TP53 mutation has led to patients who may previously have received 7 + 3, to be given azacitadine or decitabine in combination with venetoclax. Other changes to note include the approval of midostaurin in combination with standard cytarabine and daunorubicin induction therapy for patients with a FLT3 mutation in 2017. Additionally, the study design limits ability to assess long-term outcomes in patients who required third line therapy or long-term outcomes for patients unable to proceed to transplant. Finally, given the complex nature of patients disease course and overall hospitalization we are unable to conclude the impact of IDAC in the role of deaths throughout the study. These limitations restrict the generalizability of results found. Despite these limitations, this study does add to the current body of literature surrounding re-induction for AML and can aid in reducing the ambiguity in choosing a re-induction strategy.

Conflict of Interest Statement

Tara Lin, MD: Consultant for Servier and Jazz Pharmaceuticals; **Zahra Mahmoudjafari, PharmD, MBA, BCOP, FHOPA:** Advisory Board Participant for Janssen, Pfizer, and Sanofi

Authorship Contributions

SL: Conceptualization, Methodology, Validation, Investigation, Writing – Original Draft; **KW**: Conceptualization, Methodology, Validation, Resources, Writing – Review and Editing; **KB**: Validation, Resources, Writing – Review and Editing; **TL**: Validation, Resources, Writing – Review and Editing; **ZM**: Validation, Resources, Writing – Review and Editing; **VC**: Validation, Resources, Project Administration; **DG**: Formal Analysis; **KG**: Conceptualization, Methodology, Resources, Writing – Review and Editing

Data Sharing Statement

The data collected during this study will be made available upon reasonable request.

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