


# DAC and CLAM are equally effective as early second induction in newly diagnosed AML patients with persistent leukemia in early bone marrow evaluation – a retrospective study by Polish Adult Leukemia Group

Kamil Brzozowski<sup>1,2,\*</sup> , Agnieszka Pluta<sup>1,2</sup>, Martyna Włodarczyk<sup>3</sup>, Grzegorz Helbig<sup>3</sup>,  
 Małgorzata Rażny<sup>4</sup>, Tomasz Gromek<sup>5</sup>, Marek Hus<sup>5</sup>, Marta Sobas<sup>6</sup>, Łukasz Bołkun<sup>7</sup>,  
 Elżbieta Patkowska<sup>8</sup>, Andrzej Szczepanik<sup>9</sup>, Krzysztof Gawroński<sup>10</sup>, Janusz Hałka<sup>11</sup>,  
 Edyta Cichocka<sup>12</sup>, Elżbieta Wiater<sup>13</sup>, Agata Obara<sup>14</sup>, Ewa Wawrzyniak<sup>1,15</sup>,  
 Agnieszka Wierzbowska<sup>1,2</sup>

<sup>1</sup>Department of Hematology, Medical University of Lodz, Lodz, Poland

<sup>2</sup>Department of Hematology and Transplantology, Multidisciplinary Provincial Center of Traumatology and Oncology,  
 Nicolas Copernicus in Lodz, Poland

<sup>3</sup>Department of Hematology and Bone Marrow Transplantation, Medical University of Silesia, Katowice, Poland

<sup>4</sup>Department of Hematology, Rydygier Memorial Hospital, Krakow, Poland

<sup>5</sup>Department of Hematooncology and Bone Marrow Transplantation, Medical University of Lublin, Lublin, Poland

<sup>6</sup>Department of Hematology, Blood Neoplasm and Bone Marrow Transplantation,  
 Wrocław Medical University, Wrocław, Poland

<sup>7</sup>Department of Hematology, Medical University Hospital, Białystok, Poland

<sup>8</sup>Department of Hematology, Institute of Hematology and Transfusion Medicine, Warsaw, Poland

<sup>9</sup>Department of Hematology and Bone Marrow Transplantation,  
 Poznań University of Medical Sciences, Poznań, Poland

<sup>10</sup>Department of Clinical Hematology, Military Medical Academy, Warsaw, Poland

<sup>11</sup>Department of Hematology, Clinical Hospital of the Ministry of Internal Affairs and Administration  
 with the Warmia-Mazury Oncology Center in Olsztyn,  
 University of Warmia and Mazury, Olsztyn, Poland

<sup>12</sup>Department of Hematology, Multidisciplinary Provincial Center Rydygier in Torun, Poland

<sup>13</sup>Department of Hematology and Bone Marrow Transplantation, Copernicus Memorial Hospital, Torun, Poland

<sup>14</sup>Department of Hematology, Holy Cross Cancer Center, Kielce, Poland

<sup>15</sup>Cytogenetics Laboratory, Multidisciplinary Provincial Center of Traumatology and Oncology,  
 Nicolas Copernicus in Lodz, Poland

\*Address for correspondence: Kamil Brzozowski,  
 Department of Hematology, Medical University of Lodz,  
 ul. Ciołkowskiego 2, 93–510 Lodz, Poland;  
 e-mail: brzozowskikamils@gmail.com

Received: 07.08.2024 Accepted: 13.09.2024

This article is available in open access under Creative Common Attribution-Non-Commercial-No Derivatives 4.0 International (CC BY-NC-ND 4.0) license, allowing to download articles and share them with others as long as they credit the authors and the publisher, but without permission to change them in any way or use them commercially.

## Abstract

This study presents a retrospective analysis of patients with acute myeloid leukemia <60 years of age, who had  $\geq 10\%$  blasts in early bone marrow evaluation on day 14 of their first DAC (daunorubicin + AraC + cladribine) induction cycle. Patients included in this analysis were treated according to the PALG-AML-1/2012 and PALG AML-1/2016 studies. As the second early induction, 22 patients received DAC and 35 patients received CLAM (cladribine + AraC + mitoxantrone). There was no significant difference between patients treated with CLAM and those treated with DAC chemotherapy in terms of overall survival (OS after 2 years 52% vs. 76% for DAC, HR 0.68, 95% CI: 0.26–1.77,  $p = 0.4$ ). Furthermore, there was no significant difference in composite complete remission (cCR) rates between the two treatment regimens: 60% (21/35) for CLAM and 54.6% (12/22) for DAC ( $p > 0.05$ ). Both treatment regimens had a similar toxicity profile and early death rate.

**Keywords:** refractory acute myeloid leukemia, early second induction, treatment, cladribine

Acta Haematologica Polonica 2024; 55, 5: 245–251

## Introduction

Acute myeloid leukemia (AML) is a rare, aggressive and heterogeneous malignancy. Currently, 35–40% of patients aged under 60 and 5–15% of patients aged over 60 can be cured of AML using intensive chemotherapy [1, 2]. Successful treatment of AML depends on the ability to achieve complete remission (CR) and to prevent relapse. Both may be affected by the efficacy of induction chemotherapy.

Despite advances in AML treatment and the implementation of novel drugs over the last decade, the chemotherapy regimen with anthracycline and cytarabine (known as AraC) which is commonly referred to as the '3+7' regimen, has been the backbone of induction therapy since 1973 [3, 4]. Studies by the Polish Adult Leukemia Group (PALG) have demonstrated that a combination of cladribine with daunorubicin (DNR) and with AraC (collectively known as the DAC regimen) results in a significantly increased CR rate after a single induction course compared to the standard two-drug induction (DA-60) [5, 6]. The DAC arm has also been found to have a survival advantage over the DA-60 arm, particularly in patients with high-risk cytogenetics [6].

There is evidence that early blast clearance after induction chemotherapy is an important prognostic indicator of treatment outcome in addition to genetics and molecular genetics. Previous studies have shown that persistent leukemia in the bone marrow on days 14–21 of the first induction is associated with a lower likelihood of achieving CR [7–10]. Early bone marrow evaluation helps identify patients with primary refractory disease who might benefit from the prompt administration of a second induction therapy.

However, it remains an open question as to which of the available treatment options is the most beneficial [11]. In many centers, the same course of 3+7-based induction chemotherapy has been commonly used as early second induction, with CR rates ranging from 43% to 61% and an early death rate associated with induction treatment of 10% [12, 13].

Therefore, a therapeutic option better than DA as an early second induction is currently being sought. FLAG-IDA (fludarabine, high dose cytarabine, idarubicin) [14], MEC (mitoxantrone, etoposide, and high dose cytarabine) [15], HAM (mitoxantrone and high dose cytarabine) [16], and CLAM (cladribine, high dose cytarabine, and mitoxantrone) [17] have all been studied as rescue regimens when no CR was achieved after the first induction. However, as yet there has been no comparison between these cycles and standard DA therapy.

Therefore, in the presented analysis we have retrospectively compared the efficacy and safety of DAC to CLAM given as early second induction in newly diagnosed AML patients who had  $\geq 10$  blasts in bone marrow on day 14 after their first DAC induction.

## Material and methods

### Patient characteristics

Patients included in this analysis were treated according to the PALG-AML-1/2012 and PALG AML-1/2016 trials [18, 19]. Both trials included newly diagnosed AML (APL excluded) patients between the ages of 18 and 60 who were eligible for standard induction chemotherapy. In the PALG-AML-1/2012 study, all patients were given an induction cycle according to the DAC regimen (DNR 60 mg/m<sup>2</sup> *i.v.*, days 1–3, cladribine 5 mg/m<sup>2</sup> *i.v.*, days 1–5, AraC 200 mg/m<sup>2</sup> 12 h *i.v.* infusion, 2 h after cladribine infusion days 1–7) [6]. On day 14, bone marrow (BM) assessments were locally performed, and if  $\geq 10\%$  of blasts were observed in non-hypoplastic BM and if the patients were eligible to receive further chemotherapy (ECOG  $\leq 2$  and Charlson Comorbidity Index (HCT-CI)  $\leq 3$ ) [20, 21], early second induction *i.e.* CLAM (mitoxantrone 10 mg/m<sup>2</sup> 30 min *i.v.* infusion, days 1–3; cladribine 5 mg/m<sup>2</sup> 2 h *i.v.*, days 1–5; AraC 2.0 g/m 4 h *i.v.*, 2 h after cladribine infusion, days 1–5) was applied on day 16 [18]. In the PALG AML-1/2016 study, patients were randomized to either

DA-90 (DNR 90 mg/m<sup>2</sup> *i.v.*, days 1–3 and AraC 200 mg/m<sup>2</sup> 12 h *i.v.*, days 1–7) [22] or DAC induction. They were given early second induction according to the randomization arm (DA-45 or DAC) if, at day 14,  $\geq 10$  blasts in non-hypoplastic marrow were observed. Patients in complete remission (CR) after double induction were scheduled for risk-stratified post-remission treatment in both studies. Intermediate-risk and high-risk patients with a matched sibling or an unrelated donor were offered an allogeneic hematopoietic stem-cell transplantation (alloSCT) as soon as a matched donor was available. At the discretion of the physician, autologous stem cell transplantation (autoSCT) could be offered as an option for patients in the intermediate-risk group who did not have a donor. All other patients proceeded to three cycles of consolidation with AraC in a dose of 3 g/m<sup>2</sup>/bid on days 1, 3, and 5 in the PALG-AML-1/2012 study, or 2 g/m<sup>2</sup>/bid on days 1, 3, and 5 in the PALG-AML-1/2016 study. Any patients who did not respond were withdrawn from the study, and allocated to alternative salvage therapy.

Comparisons between the patients' characteristics were performed using the Mann-Whitney U test for continuous variables other than normal distribution and by the Chi<sup>2</sup> test for categorical variables with appropriate to numbers of patients' correction (V-square test, Chi<sup>2</sup> test with Yates' correction, and exact Fisher's test). To avoid type I error in multiple comparisons, Bonferroni corrections for *p*-values were used. Overall survival (OS) was defined as the time from diagnosis to death from any cause. Event-free survival (EFS) was calculated as the time from diagnosis to death or relapse, whichever occurred first. OS and EFS were estimated using the Kaplan–Meier method and compared using a log-rank test. *P* values  $< 0.05$  were considered significant. Statistical analysis was performed using R software 3.3.2. (GNU General Public License) for the Windows 11 operating system (©Microsoft Corporation).

## Results

This analysis covered only patients who had  $\geq 10\%$  of blasts in non-aplastic bone marrow at early bone marrow (BM) evaluation after their first DAC induction and who received DAC or CLAM as early second induction. In total, 57 patients were included: 22 in the DAC arm and 35 in the CLAM early second induction arm. The median age of patients was 41 (range: 19–61) and 57.9% were male. There was no difference between the DAC and CLAM groups in terms of baseline characteristics of age, gender, BM infiltration with leukemic blasts, or PB morphology, or of the etiology of AML (*i.e.* *de novo* vs. secondary) or of genetic risk group according to ELN 2010. Detailed patient characteristics are set out in Table 1.

### Response to second induction

Overall, composite CR (cCR = CR + CRi) after the second induction was achieved in 33 patients (58%); one patient

**Table 1.** Characteristics of DAC and CLAM groups

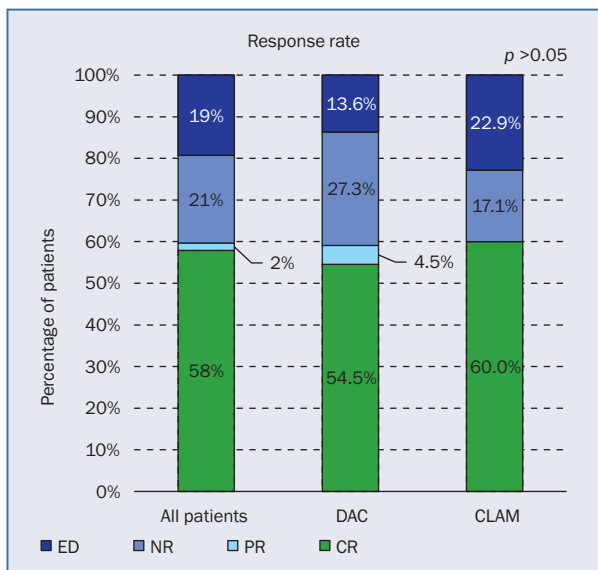
Characteristic	Overall (n = 57)	DAC (n = 22)	CLAM (n = 35)	<i>p</i>
Age (years), median (range)	41 (19–61)	44.5 (20–60)	41 (19–61)	NS
Gender, n [%]				
Female	24/57 (42.1%)	11/22 (50%)	13/35 (37.1%)	NS
Male	33/57 (57.9%)	11/22 (50%)	22/35 (62.9%)	
Bone marrow blasts %, median (range)	65 (20–100)	66 (20–100)	65 (26–95.8)	NS
Bone marrow blasts % D14, median (range)	45 (11–100)	50 (11–92)	43 (11–100)	NS
WBC, median (range)	5.49 (0.69–293)	5.995 (1.26–293)	5.49	NS
PLT, median (range)	67 (12–1.685)	62.5 (23–259)	72 (12–1.685)	NS
HGB, median (range)	8.7 (4.2–13.1)	8.85 (6.3–12.7)	8.7 (4.2–13.1)	NS
AML, n [%]				
<i>de novo</i>	50/57 (87.7%)	20/22 (90.9%)	30/35 (85.7%)	NS
secondary	7/57 (12.3%)	2/22 (9.1%)	5/35 (14.3%)	
ELN 2010, n [%]				
Low	1/48 (2.1%)	0/14 (0%)	1/34 (2.9%)	NS
Intermediate	24/48 (50%)	4/14 (28.6%)	20/34 (58.8%)	
High	23/48 (47.9%)	10/14 (71.4%)	13/34 (38.2%)	

ELN – European LeukemiaNet; HGB – hemoglobin; PLT – platelet count; WBC – white blood cells; NS – not significant

(2%) achieved PR, and 12 (21%) patients were refractory. There was no significant difference in cCR rate between the DAC and CLAM arms (54.5% vs. 60% respectively). Although resistance to early second induction was more frequent in the DAC compared to the CLAM regimen (27.3% vs. 17.1%), the difference was not significant. In contrast, the 6-week mortality rate was lower in DAC vs. CLAM early second induction (13.6% vs. 22.9%), but this was also non-significant (*p* = 0.4) (Fig. 1).

### Survival

The probability of 2-year event-free survival (EFS) was comparable between the arms (44%; 95% CI [24–80%] vs. 40% 95% CI [25–65%] respectively for DAC and CLAM regimens, as shown in Figure 2A. The probability of 2-year overall survival (OS) was higher for the DAC arm (76%;



**Figure 1.** DAC vs. CLAM response rates; CR – complete remission; ED – early death; NR – no response; PR – partial remission

95% CI [60–97%]) compared to the CLAM early second induction (52%; 95% CI [36–77%]) arm, but again the difference was not significant (see Fig. 2B).

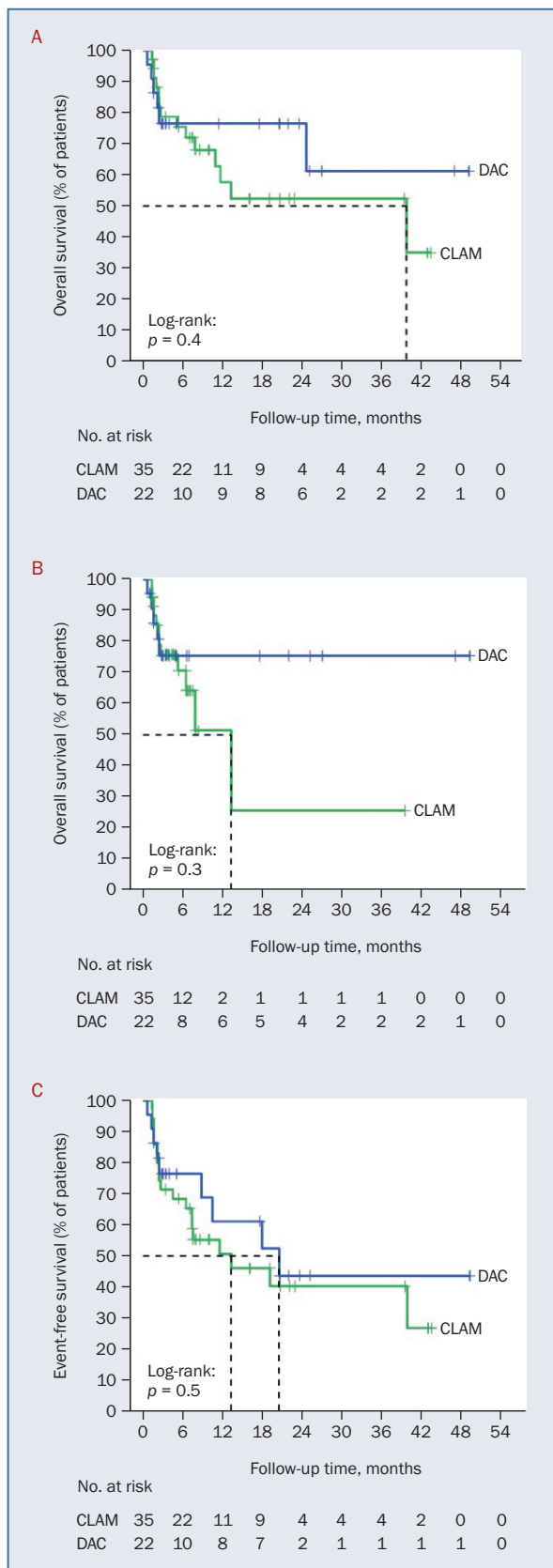
AlloSCT was performed in 19 (54.3%) patients in the DAC-CLAM cohort and in five (22.7%) patients in the DAC-DAC cohort. When the OS was censored at transplantation, median OS was 13.5 months in the DAC-CLAM group but median OS was not reached in the DAC-DAC group ( $p = 0.3$ ) (see Fig. 2C).

### Hematopoietic recovery and adverse effects

All patients experienced WHO grade 4 neutropenia and thrombocytopenia. The median time of neutrophil recovery above 0.5 G/L was 40 days, and did not differ between the CLAM and DAC early second induction arms (41 and 40 days, respectively;  $p = 0.88$ ) (see Tab. II). In addition, the duration of hospitalization and the median number of RBCs and platelet transfusions were comparable between the two regimens (see Tab. II again). Infections, mucositis, and diarrhea were the most frequent grade  $\geq 3$  nonhematological adverse events, but only diarrhea was significantly more frequent in the DAC-DAC vs. the DAC-CLAM groups (see Tab. III).

### Discussion

To date, there have been no randomized studies indicating the most effective reinduction chemotherapy for patients with resistant AML. Our study compared CLAM and DAC chemotherapy as a second early induction based on historical data of patients with a blast count  $\geq 10\%$  on day 14 after



**Figure 2.** Survival analysis DAC vs. CLAM – **A.** probability of overall survival; **B.** probability of overall survival censored on alloSCT; **C.** probability of event-free survival

**Table II.** Nonhematological toxicity for DAC and CLAM groups

Description, diagnosis, symptom	DAC (n = 22) % (n)	CLAM (n = 35) % (n)	p
Neutropenic fever	50% (11)	25.7% (9)	NS
Bacteriemia	31.8% (7)	17.1% (6)	NS
Pneumonia	4.5% (1)	17.1% (6)	NS
Sepsis	9.1% (2)	14.3% (5)	NS
COVID-19 infection	9.1% (2)	0% (0)	NS
CMV reactivation	4.5% (1)	2.9% (1)	NS
Fungemia	0% (0)	8.6% (3)	NS
Pulmonary aspergillosis	0% (0)	2.9% (1)	NS
Colitis	0% (0)	5.7% (2)	NS
Mucositis	4.5% (1)	2.9% (1)	NS
Diarrhea	36.4% (8)	2.9% (1)	*

After applying Bonferroni correction, level of statistical significance was 0.0045. Diarrhea\* was sole significantly different toxicity; NS – not significant

**Table III.** Hematological toxicity for DAC and CLAM groups

Variable, median (range)	CLAM	DAC	p
Absolute neutrophil count <0.5 G/L – number of days	41 (18–64)	40 (15–129)	NS
Packed red blood cells – units	11 (4–26)	10.5 (3–30)	NS
Platelets – units	15 (2–95)	17 (4–38)	NS
Hospitalization – number of days	41 (15–74)	37 (22–99)	NS

NS – not significant

DAC induction chemotherapy. Cladribine, in combination with mitoxantrone and cytarabine, has been the subject of previous studies [17, 23].

Our presented study retrospectively compared the efficacy and safety of DAC or CLAM given as early second induction in newly diagnosed AML patients with  $\geq 10\%$  blasts in bone marrow on day 14 after DAC induction.

Our study showed no significant differences between patients treated with DAC vs. CLAM chemotherapy in terms of overall survival (OS at 2 yrs 52% vs. 76% for DAC, HR 0.68, 95% CI 0.26–1.77,  $p = 0.4$ ) or event-free survival (EFS at 2 yrs 40% vs. 44% for DAC, HR 0.78, 95% CI 0.35–1.73,  $p = 0.5$ ). Moreover, no significant difference in cCR rates was found between the two regimens: 54.6% (12/22) for DAC and 60% (21/35) for CLAM ( $p > 0.05$ ).

Russell et al. [24] compared the effectiveness of chemotherapy in 523 older ( $> 60$ ) AML patients. Of these patients, 164 (31%) were not in CR/CRi, 260 (50%) were in CR/CRi

MRD positive, and 99 (19%) were in CR/CRi but MRD was not known. These patients were randomized to one of three arms: DA, or FLAG-IDA, or DAC (containing 193, 191, and 139 patients, respectively). In the group that did not achieve CR/CRi after course 1, 47% (78/164) achieved CR/CRi within 50 days after course 2; 55%, 57%, and 34% for DA, DAC, and FLAG-IDA, respectively (DA vs. DAC  $p = 0.63$ , DA vs. FLAG  $p = 0.015$ ). The 57% CR/CRi result for DAC as a second induction is comparable to our observations. Overall, there was no difference in 5-year OS between DA vs. FLAG-IDA (HR = 0.90, 95% CI 0.70–1.16,  $p = 0.407$ ) or DA vs. DAC (HR = 0.82, 95% CI 0.62–1.09,  $p = 0.174$ ). After excluding patients with unknown MRD, a significant long-term survival benefit was observed with intensified therapy with DAC or FLAG-IDA in a randomized comparison of DA with DAC (OS at 5 yrs 32% vs. 22% for DA; RR 0.84, 95% CI 0.77–0.98,  $p = 0.029$ ) and FLAG-IDA (OS at 5 yrs 34% vs. 23% for DA; RR 0.71, 95% CI 0.54–0.96,  $p = 0.026$ ) [24]. More significant hematological toxicity was observed with DAC or FLAG-IDA compared to DA ( $p < 0.001$  for platelet and neutrophil recovery). Day 60 mortality was increased in patients randomized to FLAG-IDA (9% vs. 4% for DA and 4% for DAC,  $p = 0.032$ ).

Ferrara et al. [25] conducted a retrospective single-center analysis assessing early second induction of the FLAG regimen in a group of patients aged under 60 with AML in whom a blast count above 10% was observed on day 15. Overall, CR was achieved in 67% (20/30), NR in 27% (8/30), and ED in 6% (2/30). The median number of days to recover neutrophil counts  $> 0.5 \times 10^9/L$  and platelets  $> 20 \times 10^9/L$  from the start of the second induction was 20 and 22 days, respectively. The median OS was 12 months. The EORTC Leukemia Cooperative Group Phase II study evaluated the effectiveness of salvage treatment consisting of an intermediate dose of cytosine arabinoside ( $2 \times 500 \text{ mg/m}^2/\text{day}$  for 7 days) and idarubicin ( $12 \text{ mg/m}^2/\text{day}$  on days 1, 3, and 5, 24-h infusion) in primary resistant AML [26]. Twenty-one patients from seven centers participated in the study. CR was achieved in 52% of patients (11/21), NR in 33% (7/21), and ED in 14% (3/21). The median OS was 10 months. The most common complications were fever (20/21), bleeding (15/21), and hepatic dysfunction (7/21). The number of days until hematological recovery, *i.e.* ANC  $> 0.5 \text{ G/L}$  and PLT  $> 20 \text{ G/L}$ , was 29 and 24, respectively.

In our study, we showed higher mortality in the group treated with CLAM compared to DAC, but the differences were statistically insignificant (22.86% (8/35) vs. 13.64% (3/22), respectively),  $p = 0.4$ . A higher incidence of neutropenic fever was found in patients treated with DAC: 50% (11/22) compared to CLAM 25.7% (9/35). Nevertheless, CLAM was associated with more frequent severe infection complications (septic shock and pneumonia) compared to DAC: for pneumonia: 17% (6/35) vs. 4.5% (1/22) and for



septic shock: 14% (5/35) vs. 9% (2/22). Walti et al. [27] showed that microbiologically documented infections occurred more frequently after CLAG-M compared to 3+7 (adjusted rate ratio, 1.65 [95% CI, 1.06–2.58];  $p = 0.03$ ), with a cumulative incidence of 27.8% and 16.5% respectively by day 90 for newly diagnosed AML. Patients receiving CLAG-M for relapsed/refractory disease had the highest cumulative incidence of 50.7%. Bloodstream infections were the most common, followed by respiratory infections. Among the 29 patients (7%) who died, infection was the primary or contributory cause of death in 59% of cases. More severe complications were most likely due to deeper neutropenia in the case of CLAG-M.

Two limitations of our analysis were the retrospective nature of the data and the small number of patients evaluated. We understand the need for caution in formulating far-reaching conclusions based on such an analysis. Even so, in the absence of prospective studies, we believe our study constitutes a welcome contribution to the discussion on selecting the most appropriate reinduction treatment.

In summary, this retrospective analysis did not show the superiority of CLAM over DAC. DAC is at least as effective in early second induction as CLAM, and could be used in daily clinical practice. Although no significant differences in OS were found between DAC and CLAM, it must be emphasized again that our study groups were small.

## Article information and declarations

### Data availability statement

The data is not publicly available. We may share data if necessary.

### Ethics statement

Both clinical trials were approved by Bioethics Committees (RNN/44/13/KE of February 19, 2013 and RNN/124/16/KE of April 19, 2016 and its update: KE/557/17 of May 16, 2017).

### Author contributions

The first and last versions of the manuscript were written by KB and AW. All authors collected patient data and cooperated on the final shape of the manuscript. AW and AP reviewed the manuscript and supervised the study.

### Funding

This study was partly supported by grant funding from the Medical University of Lodz, Poland: No. 503/1-093-01/503-11-004.

### Conflict of interest

The authors declare no conflict of interest.

## References

1. Döhner H, Weisdorf DJ, Bloomfield CD. Acute Myeloid Leukemia. *N Engl J Med*. 2015; 373(12): 1136–1152, doi: [10.1056/NEJM-ra1406184](https://doi.org/10.1056/NEJM-ra1406184), indexed in Pubmed: [26376137](https://pubmed.ncbi.nlm.nih.gov/26376137/).
2. Roboz GJ. Novel approaches to the treatment of acute myeloid leukemia. *Hematology Am Soc Hematol Educ Program*. 2011; 2011: 43–50, doi: [10.1182/asheducation-2011.1.43](https://doi.org/10.1182/asheducation-2011.1.43), indexed in Pubmed: [22160011](https://pubmed.ncbi.nlm.nih.gov/22160011/).
3. Park S, Cho BS, Kim HJ. New agents in acute myeloid leukemia (AML). *Blood Res*. 2020; 55(S1): S14–S18, doi: [10.5045/br.2020.S003](https://doi.org/10.5045/br.2020.S003), indexed in Pubmed: [32719171](https://pubmed.ncbi.nlm.nih.gov/32719171/).
4. Yates JW, Wallace HJ, Ellison RR, et al. Cytosine arabinoside (NSC-63878) and daunorubicin (NSC-83142) therapy in acute nonlymphocytic leukemia. *Cancer Chemother Rep*. 1973; 57(4): 485–488, indexed in Pubmed: [4586956](https://pubmed.ncbi.nlm.nih.gov/4586956/).
5. Holowiecki J, Grosicki S, Robak T, et al. Polish Adult Leukemia Group (PALG). Addition of cladribine to daunorubicin and cytarabine increases complete remission rate after a single course of induction treatment in acute myeloid leukemia. Multicenter, phase III study. *Leukemia*. 2004; 18(5): 989–997, doi: [10.1038/sj.leu.2403336](https://doi.org/10.1038/sj.leu.2403336), indexed in Pubmed: [14999298](https://pubmed.ncbi.nlm.nih.gov/14999298/).
6. Libura M, Bialopiotrowicz E, Giebel S, et al. Polish Adult Leukemia Group, Polish Adult Leukemia Group, Polish Adult Leukemia Group (PALG), Polish Adult Leukemia Group. A multicenter, open, non-comparative, phase II study of the combination of cladribine (2-chlorodeoxyadenosine), cytarabine, and G-CSF as induction therapy in refractory acute myeloid leukemia - a report of the Polish Adult Leukemia Group (PALG). *Eur J Haematol*. 2003; 71(3): 155–162, doi: [10.1034/j.1600-0609.2003.00122.x](https://doi.org/10.1034/j.1600-0609.2003.00122.x), indexed in Pubmed: [12930315](https://pubmed.ncbi.nlm.nih.gov/12930315/).
7. Browman G, Preisler H, Raza A, et al. Use of the day 6 bone marrow to alter remission induction therapy in patients with acute myeloid leukaemia: a leukemia intergroup study. *Br J Haematol*. 1989; 71(4): 493–497, doi: [10.1111/j.1365-2141.1989.tb06308.x](https://doi.org/10.1111/j.1365-2141.1989.tb06308.x), indexed in Pubmed: [2653407](https://pubmed.ncbi.nlm.nih.gov/2653407/).
8. Liso V, Albano F, Pastore D, et al. Bone marrow aspirate on the 14th day of induction treatment as a prognostic tool in de novo adult acute myeloid leukemia. *Haematologica*. 2000; 85(12): 1285–1290, indexed in Pubmed: [11114136](https://pubmed.ncbi.nlm.nih.gov/11114136/).
9. Kern W, Haferlach T, Schoch C, et al. Early blast clearance by remission induction therapy is a major independent prognostic factor for both achievement of complete remission and long-term outcome in acute myeloid leukemia: data from the German AML Cooperative Group (AMLCG) 1992 Trial. *Blood*. 2003; 101(1): 64–70, doi: [10.1182/blood-2002-02-0532](https://doi.org/10.1182/blood-2002-02-0532), indexed in Pubmed: [12393605](https://pubmed.ncbi.nlm.nih.gov/12393605/).
10. El Gammal MM, Owaidat HM, Rashed RA, et al. Prognostic and Therapeutic Value of Day 14 Bone Marrow Aspiration in Adult Acute Myeloid Leukemia Patients. *Clin Lymphoma Myeloma Leuk*. 2019; 19(7): e406–e413, doi: [10.1016/j.clml.2019.03.024](https://doi.org/10.1016/j.clml.2019.03.024), indexed in Pubmed: [31031147](https://pubmed.ncbi.nlm.nih.gov/31031147/).
11. National Comprehensive Cancer Network. Acute myeloid leukemia (Version 1.2024). [https://www.nccn.org/professionals/physician\\_gls/pdf/aml.pdf](https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf) (17.03.2024).
12. Othus M, Mukherjee S, Sekeres MA, et al. Prediction of CR following a second course of '7+3' in patients with newly diagnosed acute myeloid leukemia not in CR after a first course. *Leukemia*. 2016; 30(8): 1779–1780, doi: [10.1038/leu.2016.48](https://doi.org/10.1038/leu.2016.48), indexed in Pubmed: [27055872](https://pubmed.ncbi.nlm.nih.gov/27055872/).

13. Rowe JM, Kim HT, Cassileth PA, et al. Adult patients with acute myeloid leukemia who achieve complete remission after 1 or 2 cycles of induction have a similar prognosis: a report on 1980 patients registered to 6 studies conducted by the Eastern Cooperative Oncology Group. *Cancer*. 2010; 116(21): 5012–5021, doi: [10.1002/cncr.25263](https://doi.org/10.1002/cncr.25263), indexed in Pubmed: [20629023](https://pubmed.ncbi.nlm.nih.gov/20629023/).
14. de la Rubia J, Regadera A, Martín G, et al. FLAG-IDA regimen (fludarabine, cytarabine, idarubicin and G-CSF) in the treatment of patients with high-risk myeloid malignancies. *Leuk Res*. 2002; 26(8): 725–730, doi: [10.1016/s0145-2126\(02\)00003-6](https://doi.org/10.1016/s0145-2126(02)00003-6), indexed in Pubmed: [12191567](https://pubmed.ncbi.nlm.nih.gov/12191567/).
15. Visani G, Petti MC, Cenacchi A, et al. MEC (mitoxantrone, etoposide and intermediate dose cytarabine): an effective induction regimen for previously untreated acute non-lymphocytic leukemia. *Leuk Lymphoma*. 1995; 19(5-6): 447–451, doi: [10.3109/10428199509112203](https://doi.org/10.3109/10428199509112203), indexed in Pubmed: [8590845](https://pubmed.ncbi.nlm.nih.gov/8590845/).
16. Hiddemann W, Kreutzmann H, Straif K, et al. High-dose cytosine arabinoside and mitoxantrone: a highly effective regimen in refractory acute myeloid leukemia. *Blood*. 1987; 69(3): 744–749, indexed in Pubmed: [3469002](https://pubmed.ncbi.nlm.nih.gov/3469002/).
17. Wierzbowska A, Robak T, Pluta A, et al. Polish Adult Leukemia Group. Cladribine combined with high doses of arabinoside cytosine, mitoxantrone, and G-CSF (CLAG-M) is a highly effective salvage regimen in patients with refractory and relapsed acute myeloid leukemia of the poor risk: a final report of the Polish Adult Leukemia Group. *Eur J Haematol*. 2008; 80(2): 115–126, doi: [10.1111/j.1600-0609.2007.00988.x](https://doi.org/10.1111/j.1600-0609.2007.00988.x), indexed in Pubmed: [18076637](https://pubmed.ncbi.nlm.nih.gov/18076637/).
18. Pluta A, Robak T, Brzozowski K, et al. Early induction intensification with cladribine, cytarabine, and mitoxantrone (CLAM) in AML patients treated with the DAC induction regimen: a prospective, non-randomized, phase II study of the Polish Adult Leukemia Group (PALG). *Leuk Lymphoma*. 2020; 61(3): 588–603, doi: [10.1080/10428194.2019.1678151](https://doi.org/10.1080/10428194.2019.1678151), indexed in Pubmed: [31661339](https://pubmed.ncbi.nlm.nih.gov/31661339/).
19. Wierzbowska A, Pluta A, Libura M, et al. A Polish Acute Leukemia Group Prospective Multicenter Clinical Trial to Compare the Efficacy of Two Standard Induction Therapies (DA-90 vs DAC) and Two Standard Salvage Regimens (FLAG-IDA vs CLAG-M) in Acute Myeloid Leukemia (AML) Patients ≤ 60 Years Old (PALG-AML1/2016). *Blood*. 2020; 136(Supplement 1): 3–4, doi: [10.1182/blood-2020-140694](https://doi.org/10.1182/blood-2020-140694).
20. Wiernik PH, Gordon LI, Oken MM, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982; 5(6): 649–655, indexed in Pubmed: [7165009](https://pubmed.ncbi.nlm.nih.gov/7165009/).
21. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987; 40(5): 373–383, doi: [10.1016/0021-9681\(87\)90171-8](https://doi.org/10.1016/0021-9681(87)90171-8), indexed in Pubmed: [3558716](https://pubmed.ncbi.nlm.nih.gov/3558716/).
22. Fernandez HF, Sun Z, Yao X, et al. Anthracycline dose intensification in acute myeloid leukemia. *N Engl J Med*. 2009; 361(13): 1249–1259, doi: [10.1056/NEJMoa0904544](https://doi.org/10.1056/NEJMoa0904544), indexed in Pubmed: [19776406](https://pubmed.ncbi.nlm.nih.gov/19776406/).
23. Wrześniak-Kuś A, Robak T, Wierzbowska A, et al. Polish Adult Leukemia Group. A multicenter, open, noncomparative, phase II study of the combination of cladribine (2-chlorodeoxyadenosine), cytarabine, granulocyte colony-stimulating factor and mitoxantrone as induction therapy in refractory acute myeloid leukemia: a report of the Polish Adult Leukemia Group. *Ann Hematol*. 2005; 84(9): 557–564, doi: [10.1007/s00277-005-1046-0](https://doi.org/10.1007/s00277-005-1046-0), indexed in Pubmed: [15856358](https://pubmed.ncbi.nlm.nih.gov/15856358/).
24. Russell N, Thomas A, Hills R, et al. MRD Directed Treatment Intensification with Either FLAG-Ida or DA-Cladribine Improves Survival in Older AML Patients: Results from the NCR1 AML18 Randomised Trial. *Blood*. 2023; 142(Supplement 1): 830–830, doi: [10.1182/blood-2023-185956](https://doi.org/10.1182/blood-2023-185956).
25. Ferrara F, Izzo T, Criscuolo C, et al. Day 15 bone marrow driven double induction in young adult patients with acute myeloid leukemia: feasibility, toxicity, and therapeutic results. *Am J Hematol*. 2010; 85(9): 687–690, doi: [10.1002/ajh.21791](https://doi.org/10.1002/ajh.21791), indexed in Pubmed: [20652967](https://pubmed.ncbi.nlm.nih.gov/20652967/).
26. De Witte T, Suci S, Selleslag D, et al. Salvage treatment for primary resistant acute myelogenous leukemia consisting of intermediate-dose cytosine arabinoside and interspaced continuous infusions of idarubicin: a phase-II study (no. 06901) of the EORTC Leukemia Cooperative Group. *Ann Hematol*. 1996; 72(3): 119–124, doi: [10.1007/s002770050148](https://doi.org/10.1007/s002770050148), indexed in Pubmed: [8766252](https://pubmed.ncbi.nlm.nih.gov/8766252/).
27. Walti C, Halpern A, Xie Hu, et al. Infectious Complications after Intensive Chemotherapy with CLAG-M or '7+3' for Adults with Acute Myeloid Leukemia and Other High-Grade Myeloid Neoplasms. *Blood*. 2021; 138(Supplement 1): 2339–2339, doi: [10.1182/blood-2021-144908](https://doi.org/10.1182/blood-2021-144908).