Fludarabine, High Dose Cytarabine and Granulocyte Colony-Stimulating Factor (FLAG) as Consolidation Chemotherapy in Older Patients with Acute Myeloid Leukemia: A Retrospective Cohort Study

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Received: 2 November 2016 / Accepted: 6 February 2017 / Published online: 14 February 2017
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Abstract The study aimed to investigate the effect of consolidation treatment with fludarabine, high-dose cytarabine and granulocyte colony-stimulating factor or FLAG in older AML patients. The study included 41 eligible patients above 54 years old, who received both induction and consolidation chemotherapy for AML from 2008 to 2013. The study cohort had a minimum 24 months follow-up period. Survival analysis was carried out to assess patients' overall survival and disease free survival based on types of consolidation regimens. The consolidation treatment with FLAG exerted a protective effect to both overall survival and disease free survival in older patients. Patients who were consolidated with FLAG regimen had a significant longer overall survival (log-rank, $p = 0.0025$) and disease free survival (log-rank, $p = 0.0026$). The median overall survival was longer

(18.70 months) with the use of FLAG when compared to non-FLAG group (8.09 months). The median disease free survival was also longer (13.84 months) with use of FLAG when compared to the non-FLAG group (4.44 months). Regression analysis with Cox model yielded hazard ratio of 0.245 ($p = 0.0094$) in overall survival and 0.217 ($p = 0.0068$) in disease free survival. The use of FLAG as consolidation treatment was associated with approximately 60–80% reduction in hazard rates. The result was adjusted for age, race and gender in regression analysis. Older AML patients had longer remission and survival when consolidated with FLAG regimen after the induction chemotherapy.

Keywords Acute myeloid leukemia · Consolidation treatment · Cytarabine · Fludarabine · Overall survival · Disease free survival

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Introduction

Chemotherapy based on high dose infusional cytarabine (Ara-C) and anthracyclines is the primary treatment option for acute myeloid leukemia (AML). The combination is therapeutically intensive and can only be given to a clinically fit patient. Most of the AML patients need to undergo multiple cycles of chemotherapy from induction to consolidation. The induction chemotherapy aims to achieve complete remission (CR) by reducing the total leukemic cell population in the body from around 10^{12} cells to below the cytologically detectable level of about 10^9 cells. The consolidation chemotherapy is given to sustain the disease remission by eliminating the remained leukemic blasts that are undetected by the current diagnostic tests. Consolidation chemotherapy is the pre-requisite for long term survival in patients. However, the optimal regimen for

consolidation especially in older patients remains unclear [1].

The combination of fludarabine and Ara-C has been advocated as effective and safe for most refractory and relapsed AML because of higher remission rate and low toxicity profile [2–4]. The regimen is sometimes given simultaneously with granulocyte-colony stimulating factors (G-CSF) for better efficacy. The combination is called FLAG. Therapeutic effect of the FLAG can be further intensified by adding other agents into the regimen, for example mitoxantrone (Mito-FLAG), idarubicin (FLAG-Ida), amsacrine (FLAMSA), all-trans retinoic acid, etc. The potential benefits of the FLAG and its intensified versions have been evaluated in patients with refractory AML and patients with poor prognosis or unfavorable risk factors such as old age, chromosomal abnormalities and history of myelodysplastic syndrome (MDS). The study outcomes were highly appreciated [5–9].

A synergistic anti-leukemic mechanism is believed to exist among the member agents in FLAG. The presence of fludarabine increases the formation of Ara-C-5'-triphosphate (Ara-CTP), an active metabolite in the circulating leukemic blasts and this accelerates the destruction of more leukemic blasts. The presence of G-CSF stimulates the bone marrow to produce more granulocytes and stem cells. This ability in recruiting quiescent cells to S-phase could make the leukemic blasts more sensitive to Ara-CTP attack [10, 11].

Most patients who undergo induction chemotherapy will enter CR. However, the most common cause of AML death is subsequent relapse, or in another context the lack of superior consolidation regimen [12]. Most guidelines including European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) recommend standard induction chemotherapy with 3 days anthracycline and 7 days Ara-C, with or without additional agent [13, 14], but there are no recommendations about the use of FLAG as consolidation chemotherapy. This may be caused by the lack of prospective trials with the use of FLAG, as well as the number of cycles in post remission treatment. Therefore, a cohort study aimed to assess and compare the survival outcomes with regards to the use of FLAG as the consolidation chemotherapy in older AML patients is urgently needed.

Patients, Materials and Method

The retrospective cohort study was conducted at Ampang Hospital, the national referral center for hemato-malignancies and treatments in Malaysia. A total of 41 eligible patients with confirmed AML (excluding

Acute Promyelocytic Leukemia, APL) from 2008 to 2013 were identified and enrolled. Data were retrieved and analyzed after the protocol had been approved by the Medical Research and Ethics Committee and the Hospital. Characteristics of patients such as age, race, co-morbidities found at diagnosis, types of induction chemotherapy, French–American–British (FAB) subtypes and survival outcomes were summarized according to the types of consolidation regimens (FLAG and non-FLAG). The characteristics of patients are presented in Table 1.

Eligibility for study was determined based on history of remission and chemotherapy. First, a patient must undergo both induction and consolidation treatments before relapse or death. A CR must be achieved before the start of a consolidation treatment. A chemotherapy was classified as a consolidation treatment only if it was used after the attainment of CR. A CR was defined as clearance of leukemic blast in the bone marrow to less than 5% of all nucleated cells, morphologically normal hematopoiesis and return of peripheral blood cells counts to normal level [14]. Besides, we excluded patients who had received hematopoietic cell transplantation (HCT). Transplantation was a totally different treatment modality for AML and transplantation associated mortality could be a competing risk to the outcome event.

The post induction treatment response was confirmed by bone marrow aspiration and/or biopsy and full blood counts. The overall survival (OS) was measured from date of diagnosis until death of any causes, with observations censored for patients last known alive. The disease free survival (DFS) was measured from date of attainment of a CR to recurrence of AML or death of any causes [15]. The date of diagnosis, CR and event were based on date documented in the patient's electronic medical record. We defined chemotherapy related mortality as death within 30 days after chemotherapy.

The study cohort included patients with a median age at diagnosis of 61.2 years old (range, 54.1–75.3 years), majority female (58.5%) and Malay (48.8%) patients. Majority of patients (29 patients, 70.7%) were found to have at least one co-morbidity at diagnosis. Standard induction regimen with anthracycline and Ara-C was used in 39 out of 41 patients (95.1%). There were about 26 deaths (event for OS) and 27 relapses/deaths (event for DFS) found during the study period. Fifteen patients were right censored including 3 cases of loss to follow-up. The minimum follow-up duration were 24 months.

Consolidation Chemotherapy

The types of chemotherapy and the number of cycles used as consolidation are summarized and presented in Table 2.

Table 1 Characteristics of study cohort by types of consolidation treatment

Characteristics	Total (<i>N</i> = 41)		FLAG (<i>N</i> = 34)		Non-FLAG (<i>N</i> = 7)	
	<i>N</i>	(%)	<i>N</i>	(%)	<i>N</i>	(%)
1. Age at diagnosis in years, median (range)	61.2	(54.1–75.3)	61.7	(54.3–75.3)	58.7	(54.1–64.3)
2. Gender						
Male	17	(41.5)	11	(32.4)	6	(85.7)
Female	24	(58.5)	23	(67.6)	1	(14.3)
3. Race						
Malay	20	(48.8)	17	(50.0)	3	(42.8)
Chinese	15	(36.6)	13	(38.2)	2	(28.6)
Indian	6	(14.6)	4	(11.8)	2	(28.6)
4. FAB subtypes						
M2	6	(14.6)	5	(14.7)	1	(14.3)
M4	9	(22.0)	8	(23.5)	1	(14.3)
M5	6	(14.6)	5	(14.7)	1	(14.3)
M6	1	(2.4)	1	(2.9)	0	(0)
Not specified	19	(46.3)	15	(44.1)	4	(57.1)
5. Number of co-morbidities at diagnosis						
4	2	(4.9)	2	(5.9)	0	(0)
3	8	(19.5)	7	(20.6)	1	(14.3)
2	12	(29.3)	10	(29.4)	2	(28.6)
1	7	(17.0)	7	(20.6)	0	(0)
0	12	(29.3)	8	(23.5)	4	(57.1)
6. Regimens for induction treatment						
Anthracyclines + Ara-C	39	(95.2)	32	(94.2)	7	(100.0)
Anthracyclines + Ara-C + etoposide	1	(2.4)	1	(2.9)	0	(0)
Anthracyclines + etoposide + cyclophosphamide	1	(2.4)	1	(2.9)	0	(0)
7. Survival outcomes						
Alive	12	(29.3)	12	(35.3)	0	(0)
Loss to follow-up	3	(7.3)	3	(8.8)	0	(0)
Death	26	(63.4)	19	(55.9)	7	(100.0)
Chemotherapy related	6	(14.6)	4	(11.8)	2	(28.6)

Anthracyclines include mitoxantrone or daunorubicin

FAB French–American–British

Of the 41 eligible patients, 34 (82.9%) patients were consolidated with at least a cycle of FLAG and were designated as ‘FLAG’ group. The remained 7 (17.1%) patients who received other types of chemotherapy for consolidation were designated as ‘non-FLAG’ group. Among those patients in the FLAG group, 19 (46.3%) patients were further designated as ‘FLAG only’ group as they received only FLAG for consolidation and 15 patients (36.6%) were further designated as ‘combination’ group as they were consolidated with combination of FLAG and other regimens. Other regimens used in consolidation treatment were high dose Ara-C (HiDAC) and mitoxantrone plus intermittent Ara-C (MiDAC). Maintenance chemotherapy such as low dose Ara-C, thioguanine, decitabine and etoposide

were given to patients who were considered unfit for more intensive treatments. The total number (mean) of cycles of chemotherapy delivered to patients were 143 (3.5) cycles including 60 (3.2) cycles for the FLAG only group, 60 (4.0) cycles for the combination group and 23 (3.3) cycles for the non-FLAG group. The number (mean) of cycles of chemotherapy used as consolidation were 32 (1.7) cycles for the FLAG only group, 40 (2.7) for the combination group and 14 (2.0) for the non-FLAG group.

There was not specific institutional standard that determined the type of chemotherapy a patient should receive for consolidation. The choice of chemotherapy was primarily physician oriented, while considering other factors such as patient’s motivation and family supports,

Table 2 Types of chemotherapy and number of cycles used as consolidation in the study cohort

Consolidation chemotherapy	Number of patients	Cycles of induction chemotherapy (mean)	Cycles of consolidation chemotherapy (mean)	Total cycles of chemotherapy (mean)
FLAG group	34	57 (1.4)	86 (2.1)	143 (3.5)
A. FLAG only	19	28 (1.5)	32 (1.7)	60 (3.2)
a. FLAG	11			
b. FLAG-gemtuzumab	6			
c. FLAG + FLAG-gemtuzumab	2			
B. Combination	15	20 (1.3)	40 (2.7)	60 (4.0)
a. FLAG + MiDAC	4			
b. FLAG + MiDAC + HiDAC	4			
c. FLAG + maintenance	3			
d. FLAG + HiDAC	2			
e. FLAG-IDA + HiDAC + maintenance	1			
f. FLAG- gemtuzumab + HiDAC	1			
Non-FLAG group	7	9 (1.3)	14 (2.0)	23 (3.3)
a. HiDAC + MiDAC	3			
b. HiDAC + MiDAC + maintenance	1			
c. HiDAC	1			
d. DA + azacitidine	1			
e. HiDAC-Ida	1			

Maintenance includes Ara-C + etoposide, Ara-C + thioguanine or decitabine

HiDAC high dose Ara-C, *MiDAC* mitoxantrone + intermediate dose Ara-C, *DA* daunorubicin + Ara-C, *Ida* Idarubicin

cytogenetics, types of co-morbidities and so on. Patient's motivation and family supports were very crucial as intensive chemotherapy like the FLAG regimen was more likely to cause longer hospitalization and more complications.

The FLAG regimen was once used with gemtuzumab ozogamicin, a drug-linked monoclonal antibody which was marketed by Wyeth (now Pfizer) as Mylotarg from 2000 to 2010. The monoclonal antibody was withdrawn from the market in June 2010 when a clinical trial failed to demonstrate additional clinical benefit (survival time) in AML patients and observed a greater number of deaths occurred in the test group [16]. In this study, a subset of patients who received FLAG plus gemtuzumab ozogamicin for consolidation phase were also designated as 'FLAG only' group.

Statistical Analyses

The survival data was analyzed by using SAS software (version 9.4). Characteristics of patients were summarized using descriptive statistics by types of consolidation treatment (FLAG and non-FLAG). In the analysis, survival outcomes were compared between FLAG and non-FLAG, between FLAG only and non-FLAG, and between combination and non-FLAG. Kaplan–Meier product limit method was used to plot survival curves and to estimate

median survival duration. Equality of survival curves between groups was tested by using log-rank test. Bonferroni adjustment was used in multiple strata comparison for log-rank test to maintain a familywise type I error rate of 0.05.

A regression analysis with Cox proportional hazards model (Cox model) was done to estimate the effect of consolidation treatment to OS and DFS. The effect of consolidation was quantified using hazard ratio (HR) and adjusted for other explanatory covariates such as age, race and sex. To ensure valid result, the proportional hazards assumption was checked by using Cumulative Sums of Martingale Residuals and tested with Supremum test. A *p* value >0.05 would indicate that the assumption holds for the Cox model.

A HR less than one (negative regression coefficient) indicated that the use of FLAG as consolidation treatment was associated with a protective effect. Hence, the FLAG group should experience longer OS and DFS when compared to the non-FLAG group. As the HR did not translate directly into information about the duration of time until events, a ratio of median survival durations between groups should be reported [17]. For this reason, we derived the ratio of median survival durations for the FLAG, FLAG only and combination versus non-FLAG. If consolidation with FLAG regimen was truly effective, the ratio of median survival times should be greater than one.

The survival model had 6.5 events per independent variable (EPV) for OS (26 deaths divided by 4 variables) and 6.75 EPV for DFS (27 relapses/death divided by 4 variables). As both survival models had EPV values less than the rule of 10–20 EPV [18], a simulation study was conducted to assess the performance of the coefficient estimate of the treatment variable (FLAG vs. non-FLAG) at low EPV condition. The simulation study would assess the bias, deviation in variance and statistical coverage of the coefficient estimate. An EPV threshold was established for the treatment variable. The coefficient estimate was validated if the EPV threshold was less than 6.5 for OS and 6.75 for DFS.

Results

Kaplan–Meier Survival Curves and Median Survival Durations

The FLAG group consisted of patients with median age at diagnosis of 3 years older (61.7 vs. 58.7 years) and majority female (67.6 vs. 14.3%) when compared to the non-FLAG group. Majority of patients in the FLAG group suffered from at least 2 extra co-morbidities (29.4%) while majority of patients in the non-FLAG group were free of co-morbidity at diagnosis (57.1%). Chemotherapy regimens used for induction treatment in both groups were similar. Standard induction protocol with anthracyclines and high-dose Ara-C was used in more than 94% of patients in the FLAG group and all patients in the non-FLAG group (Table 1). All patients had entered CR before undergoing consolidation treatment. Among the 26 deaths in the cohort, 19 (55.9%) cases of death were from the FLAG group and 7 (100.0%) cases of death were from the non-FLAG group. The chemotherapy related mortality were 6 (14.6%) cases in total, with 4 (11.8%) cases from the FLAG group and 2 (28.6%) cases from the non-FLAG group. Within the FLAG group, 10 (52.6%) cases of death with 3 (15.8%) cases of chemotherapy related death were from the FLAG only group; 9 (60.0%) cases of death with only 1 (6.7%) case of chemotherapy related death were from the combination group.

Figure 1a shows the OS curves of the FLAG group versus non-FLAG group. The survival curves were significantly different (log-rank, $p = 0.0025$). The median OS was longer for the FLAG group when compared to the non-FLAG group (18.70 vs. 8.09 months) with a ratio of 2.31. Figure 1b shows the DFS curves of the FLAG group versus non-FLAG group. The survival curves were significantly different (log-rank, $p = 0.0026$). The median DFS was longer for the FLAG group when compared to the non-FLAG group (13.84 vs. 4.44 months) with a ratio of 3.12.

Figure 1c shows the OS curves for the FLAG only, combination and non-FLAG groups. The survival curves were significantly different (log-rank, $p = 0.0089$). The combination group had the longest median OS (24.32 months), followed by the FLAG only (17.72 months) when compared to the non-FLAG (8.09 months). When Bonferroni correction was applied, only the combination group showed significantly different OS curves from the non-FLAG group (Table 3). The ratio for median OS was 2.19 for the FLAG only group and 3.01 for the combination group, when compared with the non-FLAG group.

Figure 1d shows the DFS curves for the FLAG only, combination and non-FLAG groups. The survival curves were significantly different (log-rank, $p = 0.0102$). The combination group had the longest median DFS (14.05 months), followed by the FLAG only group (11.21 months) when compared to the non-FLAG group (4.44 months). When Bonferroni correction was applied, no significant differences were found among the three groups (Table 3). The ratio for median DFS was 2.52 for the FLAG only group and 3.16 for the combination group, when compared with the non-FLAG group.

Regression Analysis with Cox Model

Table 4 summarizes the results for both univariable and multivariable regression analysis. The assumption of proportional hazards was satisfied for all variables (Supremum test, $p > 0.05$). In the univariable regression analysis for OS, statistically significant reduction in the hazard rates was obtained in the FLAG group versus non-FLAG group (HR = 0.274, $p = 0.0046$), in the FLAG only group versus non-FLAG group (HR = 0.313, $p = 0.0216$) and in the combination group versus non-FLAG group (HR = 0.239, $p = 0.0058$). When the outcomes were adjusted for covariate differences, statistically significant reduction in hazard rates was obtained in the FLAG group versus non-FLAG group (HR = 0.245, $p = 0.0094$) and in the combination group versus non-FLAG group (HR = 0.214, $p = 0.0065$).

In the univariable regression analysis for DFS, statistically significant reduction in the hazard rates was obtained in the FLAG group versus non-FLAG group (HR = 0.277, $p = 0.0048$), in the FLAG only group versus non-FLAG group (HR = 0.302, $p = 0.0180$) and in the combination group versus non-FLAG group (HR = 0.254, $p = 0.0072$). When the outcomes were adjusted for covariate differences, statistically significant reduction in the hazard rates was obtained in the FLAG group versus non-FLAG group (HR = 0.217, $p = 0.0068$) and in the combination group versus non-FLAG group (HR = 0.201, $p = 0.0060$).

Fig. 1 The Kaplan-Meier survival curves and median survival durations in months of older AML patients consolidated with **a** FLAG and non-FLAG in OS ($p = 0.0025$). **b** FLAG and non-FLAG in DFS ($p = 0.0026$). **c** Combination, FLAG only and non-

FLAG in OS ($p = 0.0089$). **d** Combination, FLAG only and non-FLAG in DFS ($p = 0.0102$). Equality of survival distribution was tested by the log-rank test

Table 3 Multiple strata comparisons for the log-rank test

Strata comparison	Overall survival (OS)		Disease free survival (DFS)	
	Chi square	<i>p</i> value	Chi square	<i>p</i> value
FLAG only versus non-FLAG	2.6736	0.1020	3.5491	0.0823
Combination versus non-FLAG	6.0716	0.0137	5.0084	0.0214
FLAG only versus combination	0.3465	0.5561	0.0640	0.8003

Validation of the Performance of Regression Coefficients at Low EPV Ratio

The performance of the coefficient estimate of the treatment variable was checked by using a Monte Carlo simulation study. The number of outcome events in relation to the number of independent variables used in the regression analysis with Cox model for both OS and DFS did not meet the rule of 10–20 EPV [18]. Based on the results of the

simulation study, we confirmed that the Cox model required only 5–6 EPV for reliable estimation of the effect of the treatment variable for both OS and DFS. The EPV threshold was about 6 EPV. The performance of coefficient estimate became reasonably stable and was less likely to be affected by increasing EPV above this threshold. Therefore, at the current 6.5 EPV for OS and 6.75 EPV for DFS, the estimations of the treatment effect through Cox models for both OS and DFS were reliable. The low EPV

Table 4 Unadjusted and adjusted hazard ratios in OS and DFS

Comparisons	Univariable (unadjusted)		Multivariable (adjusted)	
	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
Overall survival (OS)				
FLAG versus non-FLAG	0.274 (0.112–0.671)	0.0046	0.245 (0.085–0.708)	0.0094
a. FLAG only versus non-FLAG	0.313 (0.116–0.843)	0.0216	0.389 (0.097–1.586)	0.1845
b. Combination versus non-FLAG	0.239 (0.086–0.661)	0.0058	0.214 (0.070–0.650)	0.0065
Disease free survival (DFS)				
FLAG versus non-FLAG	0.277 (0.113–0.676)	0.0048	0.217 (0.072–0.656)	0.0068
a. FLAG only versus non-FLAG	0.302 (0.112–0.814)	0.0180	0.279 (0.069–1.125)	0.0727
b. Combination versus non-FLAG	0.254 (0.094–0.691)	0.0072	0.201 (0.064–0.632)	0.0060

requirement may be caused by the strong association of the consolidation treatment with both OS and DFS. In the simulation study, the OS times were well approximated by Weibull distribution that shares the same assumption of proportional hazards with the Cox model (Results of the simulation study are available upon request).

Discussion

The consolidation treatment variable (FLAG and non-FLAG) had a strong association with both OS and DFS as shown in Fig. 1. Patients who were consolidated with at least a cycle of the FLAG regimen had a significant longer median OS and median DFS than patients who received non-FLAG regimens. Similar trend was observed for patients who received FLAG only regimen and combination regimens.

It is noteworthy that although the FLAG only group had received a lower mean cycles of chemotherapy than the non-FLAG group, patients in the FLAG only group had experienced longer median OS and median DFS than the non-FLAG group. Patients with combination regimens recorded the longest median OS and median DFS when compared to the FLAG only group and non-FLAG group. It is observed that the combination group also recorded the highest number and mean cycles of consolidation chemotherapy, followed by the non-FLAG group and FLAG only group. More cycles of intensive chemotherapy during consolidation might delay disease progression and relapse, causing longest median OS and median DFS in the combination group. However, we could not determine the causal relationship between the number of consolidation cycles and patients' survival due to limitations in the study design and sample sizes.

Lowest mortality rate was observed in the FLAG only group when compared with the combination group and non-FLAG group. However, the FLAG only group was having higher chemotherapy related mortality when compared with the combination group, but still lower than the

non-FLAG group. Majority of patients in the non-FLAG group even though did not have co-morbidities, but were not considered for more intensive chemotherapy like FLAG. This indicated that number of co-morbidity a patient presented at diagnosis was not the primary consideration for intensive chemotherapy.

A protecting effect was associated with the use FLAG regimen as consolidation treatment in older patients. This protecting effect caused significant reduction in hazards by approximately 60 to 80% and led to longer median survival in both OS and DFS. The strong variable association to the survival outcome allows the regression analysis with Cox model to reliably estimate the true effect of the FLAG regimen even at low EPV condition. Our simulation study showed that the number of outcome events was sufficient for the regression analysis with Cox model. The EPV threshold was identified at 5–6 EPV. Above the threshold, the performance of the coefficient estimate of the treatment variable was stable and less likely to be affected by increasing EPV.

Our study probably was the first to apply simulation technique to assess and validate the coefficient estimate of the treatment variable. Unlike others, the performance of Cox coefficient estimate at low EPV was checked by using a sound simulation study. Besides, we also successfully established the EPV threshold for the consolidation treatment variable, which may be used in sample size estimation for large confirmatory study. The conduct of simulation study requires technical input from a statistician and is not commonly done in clinical research involving regression analysis with Cox model.

Post induction remission have improved over years, but AML relapse remains the main cause of treatment failure. Instead of treating the patients after the relapse, the FLAG regimen and its intensified version seem being protective before the occurrence of relapse. The effectiveness of FLAG and its intensified versions relies on the enhanced intracellular conversion of Ara-C to its active metabolite Ara-CTP in the presence of fludarabine and G-CSF [19]. The enhanced killing mechanism at the intracellular level

might prevent the mutational adaptation in the remained small number of leukemic blasts that eventually leads to relapse.

In older patients, AML is highly heterogeneous and the treatment is often complicated by problems such as comorbidities, performance status, tolerance, risk of early death, pre-existing MDS and lack of motivation. Even majority of older patients up to 80 years of age can tolerate and benefit from intensive chemotherapy, less than half would eventually be treated intensively for longer survival [20, 21]. The effectiveness and toxicity profile of FLAG and its intensified versions have been investigated and reported in some clinical studies involving older patients in relapse and refractory AML, secondary AML, as well as those with poor prognosis and poor performance status. The highly appreciated outcomes warrants the use of the FLAG regimen as part of consolidation treatment for longer survival in patients. At last, the use of FLAG was not limited by cardiotoxicity found in anthracyclines, which could be detrimental to some older patients with concurrent cardiac problems. This would allow more patients to receive the consolidation treatment for longer remission and survival.

Conclusion

A significantly longer remission and survival were found when the FLAG regimen was used as part of consolidation treatment in older AML patients. By using regression analysis with Cox model, we adjusted the effect of the FLAG for covariate differences. The use of FLAG as consolidation contributed to substantial reduction in hazard rates. Therefore, the regimen should be recommended for consolidation treatment, especially for older patients who are still fit for intensive chemotherapy.

Acknowledgements The research was supported by Department of Hematology, Ampang Hospital, Clinical Research Centre, Ministry of Health and Institute of Mathematical Sciences, Faculty of Science, University of Malaya. We would also like to thank the Director General of Health Malaysia for his permission to publish the findings.

Funding This study is self-funded study.

Compliance with Ethical Standards

Conflict of interest Law Kian Boon, Dr. Chang Kian Meng, Prof. Dr. Nor Aishah Hamzah, Dr. Ng Kok Haur and Dr. Ong Tee Chuan declare that they have no conflict of interest.

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