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The Role of Anthracyclines in Acute Myeloid Leukemia Consolidation

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Abstract. *Background/Aim: This study was carried out to compare the efficacy and toxicity of consolidation with cytarabine only to consolidation with anthracycline combination in patients with acute myeloid leukemia (AML) achieving complete remission (CR). Patients and Methods: This was a multicenter, retrospective, longitudinal cohort study set between January 2010 and December 2016. Results: Generally, high-dose cytarabine Ied to better survival compared to anthracycline-containing consolidation therapy, as expected. However, for patients not undergoing hematopoietic stem cell transplantation (HSCT), anthracycline use was not necessarily associated with worse survival, depending on the number of consolidation cycles. Post-remission, pre-HSCT consolidation with high-dose cytarabine did not negatively affect survival compared to previous reports. For those without FMS-like tyrosine kinase 3 (FLT3) mutation, anthracycline use was associated with a worse survival, but for those with mutation, anthracycline use did not negatively affect survival. Conclusion: For patients who are ineligible for HSCT, selective use of anthracycline consolidation can be a viable option, while for patients with the intention of HSCT, post-remission high-dose cytarabine is a reasonable option in the absence of available donors.*

To date, the standard treatment of acute myeloid leukemia (AML) comprises induction chemotherapy to induce complete remission (CR) followed by post-remission treatment in order to improve the duration of long-term remission. In fit patients eligible for standard induction therapy, post-remission treatment after achievement of first CR (CR1) mainly consists of intensive consolidation chemotherapy (1) and allogeneic hematopoietic stem cell transplantation (HSCT) (2). The most widely accepted consolidation chemotherapy consists of repetitive cycles of high-dose cytarabine (HDAC). However, the benefit of additional chemotherapy agents, especially regarding anthracycline combination, remains a controversy. Anthracyclines are a well-known class of drugs active against AML (3) and have remained an integral component of induction chemotherapy for more than three decades. Several studies have congruously suggested a benefit from more intensive anthracycline administration during AML induction therapy (4-7), but the role of anthracyclines during consolidation therapy is poorly defined. Although Bradstock *et al.* recently reported that an increased cumulative dose of idarubicin during consolidation for adult AML resulted in improved relapse-free survival (RFS) in a phase III study (8), many studies contradicted this finding and advocate HDAC monotherapy (9-11). In addition, post-remission consolidation chemotherapy has not been shown to have a beneficial impact on outcomes after HSCT for patients with AML in CR1 if a donor is readily available (12-14). However, in real-world clinical practice, many patients are subjected to 1-2 additional cycles of consolidation chemotherapy due to lack of donor availability, and in this scenario, optimal consolidation regimens are not well established.

To this end, we carried out this study to compare the efficacy and toxicity of consolidation with cytarabine only with that of anthracycline combination therapy in patients achieving CR1 with uniform induction chemotherapy. Furthermore, we opted to explore the role of post-remission consolidation in patients undergoing HSCT.

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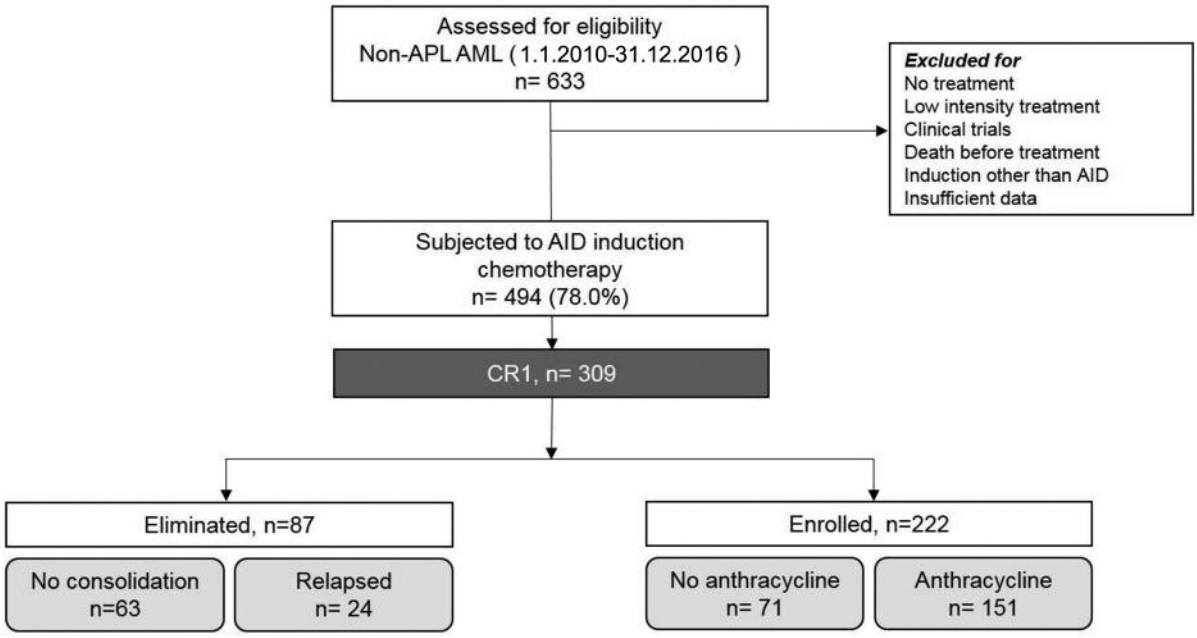

Figure 1. *CONSORT diagram.*

Patients and Methods

Study design and patients. This was a multicenter, retrospective, longitudinal cohort study of patients with AML over 16 years old treated at Seoul National University Hospital and Seoul National University Bundang Hospital. The study period was set between January 2010 and December 2016. Patients with AML achieving CR1 with standard 3+7 induction therapy and receiving at least one cycle of consolidation chemotherapy were included for analysis. Exclusion criteria included patients receiving treatments other than standard 3+7 induction therapy or no treatment. Patients with acute promyelocytic leukemia were also excluded. During the study period, 633 patients were screened, and after elimination as shown in the CONSORT diagram, a total of 222 patients were deemed eligible (Figure 1). Their medical records were reviewed and analyzed for demographics, baseline disease characteristics, chemotherapy dosing and schedule, factors related to HSCT, response to chemotherapy and HSCT, adverse events, and survival outcomes. This study was conducted according to Declaration of Helsinki and was approved by the Institutional Review Board of the participating hospitals (IRB number B-1509/314-108 for Seoul National University Bundang Hospital; J-1510-025-707 for Seoul National University Hospital).

AML diagnosis and risk stratification. The diagnosis of AML was made according to the WHO Classification of Hematopoietic Neoplasms, which requires identification of 20% or more leukemia blasts in the bone marrow (15). Secondary AML was defined as AML following myelodysplastic syndrome or myeloproliferative neoplasms confirmed prior to the diagnosis of AML, or AML secondary to proven leukemogenic exposure. Complex karyotype was defined as any karyotype with at least three chromosomal aberrations, regardless of their type and the individual chromosomes involved. Cytogenetic studies were performed at each center, whose satisfactory performance was monitored by a national external quality assurance scheme. Bone marrow cells were cultured for 24 hours then the karyotype was analyzed using the standard G-banding technique. The karyotypes were constructed and chromosomal abnormalities were reported in accordance with the International System for Human Cytogenetic Nomenclature (16). Prognostic grouping of cytogenetics was performed according to Southwest Oncology Group criteria (17). FMS-related tyrosine kinase 3 (*FLT3*) internal tandem duplication (ITD) and tyrosine kinase domain (TKD), and nucleophosmin-1 (*NPM1*) mutations were analyzed using DNA samples obtained at initial diagnosis and multiplex polymerase chain reaction. Risk stratification was mainly based on cytogenetics, and molecular abnormalities for those with available data, according to 2017 National Comprehensive Cancer Network guidelines (18).

Treatment and supportive care. Analyses were conducted overall as well as according to anthracycline use during consolidation (*i.e.* anthracycline use *versus* non-use). As mentioned above, all patients received standard 3+7 induction therapy which consisted of 12 mg/m^2 idarubicin on days 1-3 plus 100 mg/m^2 cytarabine on days 1-7. For anthracycline users, three consolidation regimens were used: (i) Daunorubicin at 45 mg/m^2 on days 1-3 plus 2 g/m^2 cytarabine on days 1-4; (ii) 12 mg/m^2 idarubicin on days 1-3 plus 2 g/m^2 cytarabine on days 1-4; and (3) HDAC (6 g/m^2) on days 1-3 plus 12 mg/m^2 idarubicin on days 1-3. The center's policy for consolidation therapy was daunorubicin/cytarabine→idarubicin/cytarabine→high-dose cytarabine-based regimen. However, the sequence of consolidation regimens and dose reduction was modified at the discretion of the attending physician. For non-anthracycline regimens, consolidation with three cycles of HDAC (3 g/m^2 twice daily over 3 days) was used.

Table I. *Baseline characteristics*.

		Anthracycline			
		Total	With	Without	*p*-Value
	Total	222	151	71	NA
Year of diagnosis, n (%)	2010-2013	146 (65.8)	133 (88.1)	13 (18.3)	<0.001
	2014-2016	76 (34.2)	18 (23.7)	58 (81.7)	
Age, years	Median (range)	51 (17-77)	50 (18-77)	54 (17-77)	0.170
	<60 Years, n (%)	165 (74.3)	118 (78.1)	47 (66.2)	0.057
	≥60 Years, n (%)	57 (25.7)	33 (21.9)	24 (33.8)	
Gender, n (%)	Male	114 (51.4)	82 (54.3)	32 (45.1)	0.199
Type of leukemia, n (%)	*De novo*	205 (92.3)	140 (92.7)	65 (91.5)	0.761
	Secondary	17 (7.7)	11 (7.3)	6 (8.5)	
Cytogenetic risk, n (%)	Low	51 (23.0)	33 (21.9)	18 (25.3)	0.835
	Intermediate	140 (63.0)	97 (64.2)	43 (60.6)	
	High	31 (14.0)	21 (13.9)	10 (14.1)	
Combined risk, n (%)*	Low	64 (28.8)	40 (26.5)	24 (33.8)	0.354
	Intermediate	91 (41.0)	61 (40.4)	30 (42.3)	
	High	32 (14.4)	22 (14.6)	10 (14.1)	
	Unknown	35 (15.8)	28 (18.5)	7 (9.8)	
Extramedullary involvement	Yes, n (%)	20 (9)	9 (6.0)	11 (15.5)	0.021
Laboratory findings, mean ± SD	BM blasts, %	60.6±26.8	61.7±27.4	58.4±25.4	0.398
	WBC count, 10^3/l	26,419±54,205	29,021±55,132	20,678±52,038	0.293
	Platelet count, 10^9/l	83.3±84.2	83.1±89.2	83.9±72.6	0.123
	Hb, g/dl	8.7±1.9	8.5±1.7	8.9±2.1	0.947

NA: Not applicable; BM: bone marrow; WBC: white blood cell; Hb: hemoglobin. *Combined risk refers to risk stratification based on cytogenetic and molecular study results.

Primary fungal prophylaxis with posaconazole at induction was uniformly applied to patients undergoing treatment after April 2015 as reimbursement was granted. Antifungal prophylaxis was not routinely used during consolidation therapy. Secondary fungal prophylaxis was provided to patients with history of fungal infection during induction.

Statistical analysis. The overall survival (OS) and RFS curves were estimated using the Kaplan–Meier method. OS was defined as the time from the date of diagnosis to death from any cause. RFS was derived from the date of CR1 to that of relapse or death from any cause. If patients survived without relapse, RFS was censored on the latest date of follow-up when no relapse was confirmed. Cox proportional hazards model and logistic regression were used to identify significant prognostic indicators for survival. Treatment-related mortality (TRM), and treatment-related toxicity were also analyzed. Chemotherapy-related mortality was defined as mortality during consolidation chemotherapy, while HSCT-related mortality was defined as death due to any cause in the absence of relapse or progression of primary disease, including infection, toxicity, and other non-relapse- or disease progression-related causes of death. Time to absolute neutrophil count (ANC) recovery was defined as the interval between the date of starting chemotherapy to the third day when ANC remained over 500/mm^3 without granulocyte colony-stimulating factor support. Time to platelet recovery was defined as the interval between chemotherapy start date to the third day when the platelet count remained over 20×10^9/l without transfusion. Differences between groups were assessed using Student's *t*-test or one-way analysis of variance for continuous variables, and Pearson chi-square test for categorical variables, as appropriate. All data were analyzed using the Statistical Package for the Social Sciences software (IBM® SPSS® statistics, version 20.0; IBM, Armonk, NY, USA). *p*-Values of less than 0.05 was considered to be statistically significant.

Results

Patient characteristics. Table I represents the baseline characteristics of all enrolled patients, including 151 prescribed anthracycline and 71 not. The median age was 51 years (range=17-77 years) and 92% had *de novo* AML. There were no significant differences between the two groups with regards to age, sex, type of leukemia, cytogenetic risk, and baseline laboratory findings. Approximately 20% of the patients had low-risk AML by cytogenetic risk group, 60% had intermediate-risk AML and 14% had high-risk AML. Among 51 patients classified as low risk group, 1 patient with inv(16) had *KIT* mutation and was thus re-classified as being at intermediate-risk. Among 140 patients classified in the intermediate-risk group, 14 patients were re-classified as low risk group for $NPM1^+/FLT3^-$ (n=12) or CCAAT enhancer binding protein alpha $(CEBPA)^+$ (n=2). On the other hand, one patient was re-classified as having high risk for harboring FLT3–TKD. The overall incidence of extramedullary disease at the time of AML diagnosis was 9%, with a higher rate in those not given anthracyclines (15.5 *vs*. 6.0%, $p=0.02$). The

Table II. *Treatment schema*.

		Anthracycline			
		Total	With	Without	*p*-Value
CX cycles	Median	2	2	2	0.220
	1, n (%)	60±27.0	39±25.8	21±29.6	
	2, n (%)	64±28.8	49±32.5	15±21.1	
	3, n (%)	98±44.1	63±41.7	35±49.3	
Induction to CR, days	Mean±SD	31.7±9.9	31.8±10.1	31.6±9.5	0.922
Induction to 1st CX, days	Mean±SD	62.2±17.1	65.1±15.1	55.9±19.3	<0.001
Upfront HSCT, n (%)	Frequency	66 (29.7)	39 (25.8)	27 (38.0)	0.064
HSCT Donor, n (%)	Matched related	37 (56.1)	22 (56.4)	15 (55.6)	0.468
	Matched unrelated	16 (24.2)	11 (28.2)	5 (18.5)	
	Other*	13 (19.7)	6 (15.4)	7 (25.9)	
HSCT Conditioning, n (%)	Myeloablative	14 (21.1)	9 (23.1)	5 (18.5)	0.656
	Reduced intensity	52 (78.8)	30 (76.9)	22 (81.5)	

CX: Consolidation therapy; CR: complete remission; HSCT: hematopoietic stem cell transplantation; NA: not applicable. *Including mismatched related donors and cord blood.

sites involved were: Lymph nodes in six, brain in four, cerebrospinal fluid in three, soft tissue in two, pleural effusion in one, liver in one, and other solid organ involvement in three.

Treatment schema of consolidation treatment. Both groups received a median of two cycles of consolidation chemotherapy (Table II). There were 60 patients (27.0%) who received only one cycle of consolidation chemotherapy (Table II). Among them 46 (76.7%) were subjected to upfront HSCT (Table III). Among 14 patients who did not undergo HSCT, reasons for only receiving one cycle of consolidation chemotherapy were as follows: Death during consolidation in two; hepatitis B reactivation in one; patient refusal in 11. Approximately 30% of patients underwent upfront HSCT and the rate was higher in those not receiving anthracycline, although not without statistical significance (38.0% *vs*. 29.7%, $p=0.064$). Among patients with high cytogenetic risk, 45% underwent upfront HSCT, with a comparable rate between the two groups (no anthracycline *vs*. anthracycline, 50% *vs*. 43%). Seventeen patients with high cytogenetic risk did not undergo HSCT because they were too old for (*i.e*. older than 65 years old at diagnosis; n=5), had no suitable donors (n=7), refused HSCT (n=2), died during consolidation (n=2), or were transferred to another hospital (n=1).

The median number of cycles of consolidation chemotherapy before upfront HSCT was one in both groups. There was no difference between those treated with anthracycline and those not with regard to time to CR (31.8 *vs*. 31.6 days, respectively, $p=0.922$), but those receiving anthracycline were subjected to delay of by approximately 9 days in delivery of consolidation therapy (time interval between induction to first consolidation therapy: 65.1 *vs*. 55.9 days, respectively, $p<0.001$).

Table IV presents the cytarabine dose delivered to patients in each group during consolidation. For those not administered anthracycline, there were 21 patients who received one cycle of consolidation, 15 patients received two cycles, and 35 patients received three cycles. For those given anthracycline, there were 39 patients receiving one cycle of consolidation, 49 receiving two cycles and 63 patients receiving three cycles. More cytarabine was delivered during the third cycle of consolidation, as per the center's policy on consolidation treatment schema. When compared, more cytarabine was delivered to those not given anthracycline during the first consolidation (mean dose 15.9 g/m^2 *vs*. 8.0 g/m^2 for those not, $p<0.001$) and the second (mean dose 12.9 g/m^2 *vs*. 9.2 g/m^2, $p<0.001$). There were no differences in the cytarabine dose delivered during the third consolidation ($p=0.538$). The dose of idarubicin delivered to anthracycline users is presented in Table V.

Adverse events during consolidation chemotherapy. As shown in Table VI, there were more deaths in those treated with anthracycline, but there were no differences in TRM between the two groups. The most common cause of TRM during consolidation was fungal infection (n=7). There was one patient who died of intracranial hemorrhage associated with thrombocytopenia, and one who died of ischemic colitis. There were seven mortalities related to upfront HSCT. Three patients died of infection, two patients due to engraftment failure, and two of complicated graft-*versus*-host disease.

There were more bacterial infection events in those given anthracyclines during the first consolidation (Table VI). As for fungal infection, there were no differences between the two groups. The majority of those not receiving anthracycline received primary fungal prophylaxis with posaconazole during induction chemotherapy (Table VII). Anthracycline use was

Table III. *Characteristics of patients undergoing hematopoietic stem cell transplantation.*

		Anthracycline			
		Total	With	Without	*p*-Value
	Total	66	39	27	NA
Age, years	Median (range)	46 (18-63)	46 (18-63)	46 (21-63)	0.772
Cytogenetic risk, n (%)	Low	9 (13.6)	2 (5.1)	7 (25.9)	0.086
	Intermediate	43 (65.2)	28 (71.8)	15 (55.6)	
	High	14 (21.2)	9 (23.1)	5 (18.5)	
CR1 to HSCT, days	Median (range)	103.5 (17-282)	109 (62-276)	99 (17-282)	0.068

CR1: First complete remission; HSCT: hematopoietic stem cell transplantation; NA: not applicable.

Table IV. *Cytarabine dose according to consolidation step and number of consolidations. Data are mean/median (range).*

		Consolidation			
Anthracycline	Consolidation#	1st	2nd	3rd	Total
Without	1 (N=21)	15.9/18.0 (8.0-18.0)	NA	NA	15.9/18 (8.0-18.0)
	2 (N=15)	12.5/15.0 (8.0-18.0)	12.9/13.9 (4.0-18.0)	NA	25.5/29.0 (16.0-36.0)
	3 (N=35)	14.6/15.0(7.5-18.0)	14.2/12.0 (9.0-18.0)	13.5/12.0 (4.0-18.0)	42.5/36 (25.5-54.0)
	Per step	14.8/15.0 (7.5-18.0)	13.8/12.0 (4.0-18.0)	13.5/12.0 (4.0-18.0)	NA
		(N=71)	(N=50)	(N=35)	NA
With	1 (N=39)	8.0/8.0 (8.0-8.0)	NA	NA	8.0/8.0 (8.0-8.0)
	2 (N=49)	7.6/8.0 (3.0-8.0)	7.8/8.0 (0.14-18.0)	NA	15.4/16 (7.0-26.0)
	3 (N=63)	8.2/8.0 (4.0-18.0)	9.2/8.0 (4.0-18.0)	13.0/12.0 (2.0-18.0)	30.5/32.0 (12.0-32.0)
	Per step	7.9/8.0 (3.0-18.0)	8.6/8.0 (0.14-18.0)	13.0/12.0 (2.0-18.0)	NA
		(N=151)	(N=112)	(N=63)	NA

#Number; NA: not applicable.

Table V. *Idarubicin* dose according to consolidation step and number of consolidation for anthracycline users. Data are mean/median (range).*

	Consolidation			
Cosolidation#	1st	2nd	3rd	Total
1 (N=39)	30.0/27 (27.0-36.0)	NA	NA	65.3/63.0 (57.0-72.0)
2 (N=49)	28.9/27 (12.0-36.0)	30.1/36 (0-36.0)	NA	93.2/99.0 (54.0-108.0)
3 (N=63)	29.9/27.0 (0-36.0)	31.3/36.0 (0-36.0)	20.9/27.0 (0-36.0)	117.6/126 (60.0-144.0)
Per step	29.6/27.0 (0-36.0)	30.8/36 (0-36.0)	20.9/27.0 (0-36.0)	NA
	(N=151)	(N=112)	(N=63)	

#Number; NA: not applicable. *Conversion rate: daunorubicin=1, idarubicin=5, mitoxantrone=4.

also associated with longer hospital stay, longer time to ANC recovery and longer time to platelet recovery (Table VI). This trend was most prominently observed during the second cycle of consolidation chemotherapy.

Treatment schema after relapse. There were more relapses in those administered anthracyclines (62.3% *vs*. 43.7%, p=0.009). After relapse, 84.0% of the patients underwent salvage treatment: 80.8% of the patients received either standard re-induction or low-intensity chemotherapy, while 3.2% of the patients underwent salvage HSCT without re-induction (Table VIII). There were no differences in the rates of re-induction, salvage HSCT, and CR2 achievement between those administered anthracycline and those not.

Table VI. *Adverse events during consolidation*.

Event		Anthracycline			
		Total	With	Without	*p*-Value
Death	Any cause, n (%)	98 (44.1)	83 (55.0)	15 (21.1)	<0.001
	Before 1st relapse, n (%)	22 (9.9)	17 (11.3)	5 (7.0)	0.316
	TRM, n				
	During CX	16	12	4	
	Related to CX	9	7	2	
	Related to upfront HSCT	7	5	2	
	Other cause, n	–	6	5	1
Bacteremia, n (%)	1st CX (N=222)	80 (36.0)	62 (41.1)	18 (25.4)	0.023
	2nd CX (N=162)	78 (48.1)	57 (50.9)	21 (42.0)	0.295
	3rd CX (N=98)	38 (38.8)	24 (38.1)	14 (40.0)	>0.99
Fungal infection, n (%)	1st CX (N=222)	12 (5.4)	10 (6.6)	2 (2.8)	0.242
	2nd CX (N=162)	13 (8.0)	12 (10.7)	1 (2.0)	0.059
	3rd CX (N=98)	5 (5.1)	4 (6.3)	1 (6.3)	0.452
Mean hospitalization±SD, days*	1st CX (N=222)	27.0±11.3	28.3±13.1	24.1±5.1	0.009
	2nd CX (N=162)	32.3±13.4	35.9±14.5	24.3±4.7	<0.001
	3rd CX (N=98)	28.4±11.3	30.5±13.4	24.6±3.4	0.012
Mean time to ANC recovery±SD, days	1st CX (N=222)	18.6±5.6	18.4±5.8	18.9±5.3	0.567
	2nd CX (N=162)	22.9±10.4	24.9±11.1	17.4±4.5	<0.001
	3rd CX (N=98)	21.3±8.1	21.9±9.6	20.2±4.4	0.322
Mean time to platelet recovery±SD, days	1st CX (N=222)	20.4±8.7	21.0±9.6	18.7±5.1	0.046
	2nd CX (N=162)	26.4±15.4	29.6±16.6	17.4±4.5	<0.001
	3rd CX (N=98)	23.4±15.3	24.7±16.3	20.6±12.8	0.212

TRM: Treatment-related mortality; HSCT: hematopoietic stem cell transplantation; COD: cause of death; CX: consolidation therapy; ANC: absolute neutrophil count. *Unknown COD (N=5), death from secondary malignancy (N=1). Time to ANC recovery refers to the time interval between chemotherapy start to the third day of ANC >500/mm^3 without granulocyte colony-stimulating factor support. Time to platelet recovery refers to the time interval between chemotherapy start to the third day of platelet count >20×10^9/l without transfusion.

Table VII. *Fungal prophylaxis*.

	Anthracycline, n (%)			
	Total	With	Without	*p*-Value Total
Diagnosed after April 2015*	42 (18.9)	2 (1.3)	40 (56.3)	<0.001
During induction (N=222)	42 (18.9)	2 (1.3)	40 (56.3)	<0.001
During 1st consolidation (N=222)	12 (5.4)	10 (6.6)	2 (2.8)	0.242
During 2nd consolidation (N=162)	17 (10.6)	15 (13.5)	2 (4.0)	0.069
During 3rd consolidation (N=98)	14 (14.3)	12 (19.0)	2 (5.7)	0.071

*The date of reimbursement issued for primary posaconazole prophylaxis for patients undergoing induction.

Survival outcomes. The median follow-up duration for the whole cohort was 31 months (34.6 months for the anthracycline group and 29 months for the non-anthracycline group), the estimated 3-year OS rate was 61.3% and RFS was 34.9%. The RFS was significantly shorter in those administered anthracyclines (median=13.5 *vs*. 35.5 months, p=0.014; Figure 2A). On multivariate analysis, anthracycline administration was identified as significant negative prognostic factor for RFS [hazard ratio (HR)=1.732, 95% confidence intervaI (CI)=1.155-2.598, p=0.008; Table IX]. High cytogenetic risk and no upfront HSCT were also recognized as prognostic factors for poorer RFS.

The OS was also significantly shorter in those administered anthracyclines (median=38.7 *vs*. 62.1 months, p=0.001; Figure 2A). On multivariate analysis, anthracycline use, age, and cytogenetic risk group were identified as prognostic factors for OS (Table IX).

Table VIII. *Treatment schema after relapse*.

		Anthracycline, n (%)			
		Total	With	Without	*p*-Value
Actual relapse		125 (56.3)	94 (62.3)	31 (43.7)	0.009
Treatment after relapse					0.540
Chemotherapy		101 (80.8)	74 (78.7)	27 (87.1)	
Standard re-induction		97	71	26	
Low intensity chemotherapy*		4	3	1	
HSCT without induction chemotherapy		4 (3.2)	3 (3.2)	1 (3.2)	
No treatment		20 (16.0)	17 (18.1)	3 (9.7)	
CR2 achievement	Yes	70 (57.9)	52 (57.1)	18 (60.0)	0.950
HSCT	Yes	57 (47.1)	44 (48.4)	13 (43.3)	0.633
Salvage		50 (87.7)	39 (88.6)	11 (84.6)	
2nd[#]		7 (12.3)	5 (11.4)	2 (15.4)	

HSCT: Hematopoietic stem cell transplantation; CR2: second complete remission. *Salvage chemotherapy included hypomethylating agents and low-dose cytarabine treatment. [#]Refers to the patients who underwent upfront HSCT.

Table IX. *Univariate and multivariate analysis using Cox regression for relapse-free survival (RFS) and overall survival (OS)*.

	RFS				OS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age								
≥60 vs. <60 Years	1.549 (1.080-2.222)	0.018	1.426 (0.975-2.084)	0.067	1.777 (1.158-2.727)	0.009	1.966 (1.272-3.036)	0.002
Cytogenetic risk								
High vs. non-high	2.254 (1.466-3.467)	<0.001	2.459 (1.581-3.824)	<0.001	2.335 (1.449-3.763)	<0.001	2.344 (1.451-3.787)	0.001
Anthracycline								
Yes vs. no	1.615 (1.095-2.382)	0.016	1.732 (1.155-2.598)	0.008	2.438 (1.400-4.246)	0.002	2.849 (1.621-5.009)	<0.001
Upfront HSCT								
Yes vs.no	0.538 (0.359-0.807)	0.003	0.573 (0.377-0.869)	0.009	0.881 (0.565-1.372)	0.575	NA	NA

HR: Hazard ratio; CI: confidence interval; HSCT: hematopoietic stem cell transplantation; NA: not applicable.

When patients were further divided into four groups according to anthracycline use and upfront HSCT (Figure 2B), those undergoing HSCT who had not received anthracycline had the longest RFS (median RFS not reached), followed by those treated with anthracycline undergoing HSCT (26.6 months, p=0.054) compared to those not treated with anthracycline undergoing HSCT, those not treated with anthracycline and not receiving HSCT (17.9 months, p=0.015) and those treated with anthracycline not receiving HSCT (12.7 months, p=0.001). Interestingly, OS patterns were different from RFS patterns, and those not administered anthracyclines had better survival compared to those receiving them, regardless of history of upfront HSCT. Among those not given anthracyclines, there was no difference with regards to OS between those undergoing upfront HSCT and those not (p>0.99); similarly, in those given anthracycline, there was also no difference in OS according to HSCT (p=0.885).

Discussion

Generally, HDAC led to better survival compared to anthracycline-containing consolidation, as expected. However, we noted some interesting findings with anthracycline use during consolidation. Namely, we recognized that the use of anthracycline has different effects in patients undergoing upfront HSCT *versus* those not undergoing HSCT. For patients who ultimately underwent HSCT after receiving post-remission consolidative chemotherapy, anthracycline use negatively affected the outcomes. However, for patients who did not undergo HSCT, anthracycline use was not necessarily associated with worse RFS (17.9 months without anthracycline *vs*. 12.7

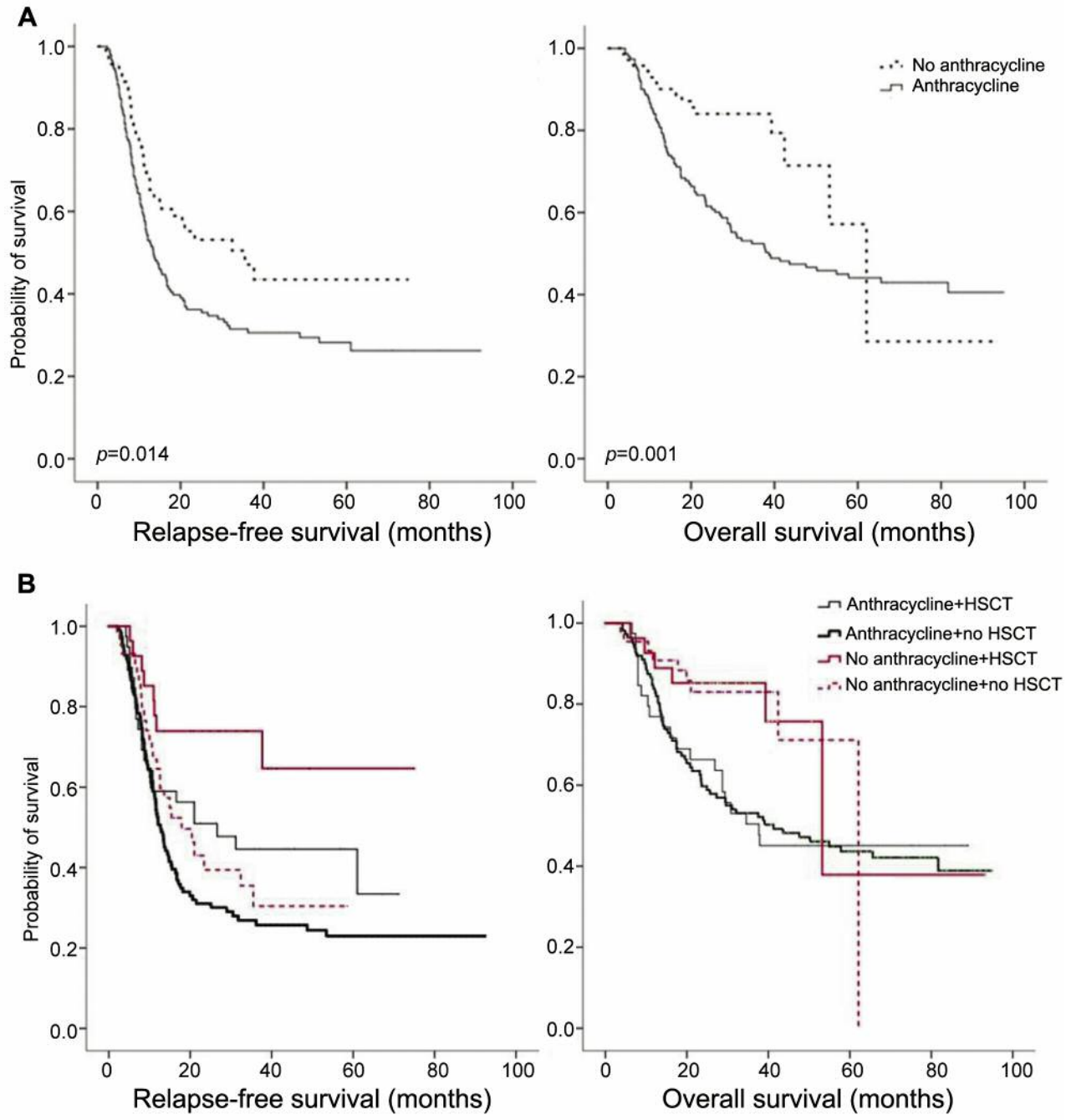

Figure 2. *Relapse-free survival and overall survival according to anthracycline use (A) and anthracycline use and upfront hematopoietic stem cell transplantation (B).*

months with anthracycline, p=0.197; Figure 2B). When the number of consolidation was considered, patients who received three cycles of consolidation therapy had longer RFS (median=17.6 months) than those who received only one cycle (median=5.7 months), as expected. Among patients who received only one cycle of consolidation therapy, those not treated with anthracyclines had better RFS than those who were (median=7.8 *vs*. 5.2 months, respectively, p=0.047). Interestingly however, for patients receiving two cycles of consolidation, those receiving anthracycline had slightly better RFS (median=6.9 *vs*. 11.6 months, respectively, p=0.102) and, for patients receiving all three cycles of consolidation therapy there were no differences in RFS (median=16.7 *vs*. 21 months, respectively, p=0.414). Based on these findings, for patients

without planning for HSCT, anthracycline-based consolidation can be used as an alternative option for those who cannot tolerate HDAC due to side-effects or who cannot complete all three cycles of consolidation for whatever reason.

Another interesting observation is on OS and its prognostic factors. As mentioned above, for patients not undergoing HSCT, anthracycline use seemingly had little effect on RFS. However, for the same subgroup of patients, those treated with anthracycline had significantly worse OS (Figure 2B). Although the rates of CR2 achievement and salvage HSCT were not different between the two groups, we speculate that this discrepancy is due to the quality of CR2. Given that those receiving anthracycline were more recently treated and thus had access to better salvage chemotherapy options and supportive care, these patients might have had a deeper response and longer second RFS. This might also explain why upfront HSCT was not a prognostic factor for OS (Table IX) in our cohort.

Regarding the issue of post-remission pre-HSCT consolidation therapy, only a limited amount of data is available to help guide this decision. Since all patients enrolled in our study received at least one cycle of consolidation therapy before HSCT, we cannot make a direct comparison with patients undergoing HSCT without consolidation. However, survival outcomes of our patients (estimated 3-year OS of 60.7%, RFS rate of 51.9% for patients undergoing upfront HSCT) were comparable to those of previous studies (12, 19), and based on this we can assume that consolidation at least did not negatively affect the survival outcomes of the patients. Especially since most of our patients underwent HSCT with reduced intensity conditioning, some might have benefited from potential additive effects of post-remission consolidation in the absence of readily available donors. Furthermore, our results suggest that if upfront HSCT is delayed and consolidation is needed, HDAC seems to be a reasonable choice. Although we cannot suggest a definite cutoff for the optimal cumulative dose of cytarabine, adequate delivery of cytarabine seems to play an important role in survival outcomes, and those who cannot tolerate HDAC should receive additional chemo-agent(s) as compensation.

Besides the obvious pitfall of being a retrospective study, another major limitation of our study is the lack of molecular and genetic data. However, there were 112 patients with *FLT3* mutation status available, and the role of anthracycline-based consolidation was evaluated in this subgroup of patients. Out of 91 patients without *FLT3* mutation, 56 were treated with anthracycline. When survival was compared, those not treated with anthracycline had longer RFS (median=35.5 *vs*. 15.5 months, respectively, p=0.088) and significantly longer OS (81.7 *vs*. 41.3 months, respectively, p=0.009). On the other hand, there were 21 patients with FLT3 mutation and as whole, survival of these patients was significantly shorter compared to patients without *FLT3* mutation. Interestingly, there were no differences according to anthracycline therapy with regards to RFS (9.6 *vs*. 6.2 months, respectively, p=0.437) and OS (30.8 *vs*. 12.4 months, respectively, p=0.605). Since there were only 10 treated with anthracycline and 11 not, the number of patients was too small to draw definitive conclusions, but the role of daunorubicin in this subset of patients deserves attention not only during induction (20), but also during consolidation.

We feel that one of the strengths of our study is how accurately it represents real-world practice, where patients are subjected to at least one cycle of consolidation regardless of intended HSCT due to many barriers, including a lack of readily available donors. For patients assigned to HSCT with reduced intensity conditioning, bridging HDAC consolidation may have an additive role in better RFS. Finally, for patients who are ineligible for HSCT, selective use of anthracycline consolidation seems to be a viable option.

Conflicts of Interest

There are no conflicts of interest to disclose regarding this study.

Authors' Contributions

Design of the study: Ja Min Byun, Jeong-Ok Lee. Patient enrollment and data collection: All Authors. Data analysis: Ja Min Byun, Koung Jin Suh, Jeong-Ok Lee. Wrote the article: Ja Min Byun, Jeong-Ok Lee. Revised the article: All Authors.

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