



Early removal of central venous catheter may not impact the in-hospital mortality in patients with acute leukemia

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Abstract

Central venous catheters (CVCs) are generally required for chemotherapy in patients with acute leukemia, but catheter-related infection is one of the common causes of neutropenic fever. We investigated the in-hospital mortality according to early removal of CVCs and the factors influencing the mortality in patients with acute leukemia undergoing remission induction chemotherapy. This study retrospectively analyzed the hospital record data of 278 patients with acute leukemia treated with non-tunneled CVCs and remission induction chemotherapy in a single institution. Bloodstream infection was more common ($p < 0.0001$) and median peak C-reactive protein (CRP) levels after neutropenic fever were significantly higher (23.3 vs. 14.5 mg/dl, $p = 0.003$) in the group with early removal than in the group with maintenance of the CVC. Multivariate analysis of the patients revealed a significant decrease in the mortality with female gender (odds ratio (OR): 0.19, 95% confidence interval (CI): 0.06–0.54, $p = 0.002$) and a significant increase in the mortality according to the peak CRP (OR 1.12, 95% CI: 1.07–1.17, $p < 0.0001$). By contrast, early removal of the CVC had no significant effect on the mortality (OR = 1.16, 95% CI: 0.54–2.47, $p = 0.706$) in univariate analysis. Furthermore, subsequent bloodstream infection after clinical decision for maintenance or early removal of the CVC was confirmed more frequently in the group with early removal (early removal, 22.6%; maintenance, 7.6%, $p < 0.0001$). Early removal of the CVC had no benefit regarding the mortality and prophylaxis of bloodstream infection in patients with acute leukemia undergoing remission induction chemotherapy. Therefore, maintaining a CVC for as long as possible may be considered, if catheter-related bloodstream infection is not strongly suspected.

Keywords Central venous catheter · Acute leukemia · Fever · Chemotherapy

Introduction

Neutropenic fever is a common and possibly life-threatening complication encountered during chemotherapy for acute leukemia, and it necessitates immediate hospitalization and empirical antibiotic treatment [1, 2]. A previous study on patients with leukemia reported mortality rates of 14.3%, mean lengths of hospitalization in leukemia of about 20 days, and mean costs of hospitalization above 30,000

dollars for neutropenic fever [3]. Patients with hematologic disorders, such as leukemia and lymphoma, generally require a medium- or long-term central venous catheter (CVC) for administration of chemotherapeutic agents and antimicrobials, blood product transfusion, or stem cell transplantation [4, 5]. However, the CVC is a major source of bloodstream infections in neutropenic patients with hematologic disorders [6–8].

The terms central line-associated bloodstream infection (CLABSI) and catheter-related bloodstream infection (CRBSI) are frequently used interchangeably in clinical situations, but their definitions differ [9]. CLABSI is defined as the appearance of a bloodstream infection (BSI) in a patient having a central line within 48 h without evidence of another infection site [10, 11]. By contrast, definitive CRBSI is diagnosed when the same organism grows from at least one percutaneous blood culture and a catheter tip culture, when a blood sample culture from the catheter hub has at least a

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threefold greater colony count than a blood sample culture from a peripheral vein, or when growth of microbes from a catheter hub blood sample is detected at least 2 h before growth from a peripheral vein sample [12]. One study has also shown that less than half of the patients with a CLABSI had a definitive CRBSI in the patients with malignancy [13].

To our knowledge, no study has yet evaluated the difference in the in-hospital mortality between early CVC removal due to neutropenic fever and maintenance of the CVC in patients with acute leukemia undergoing remission induction chemotherapy. In this study, our aim was to investigate whether early removal of CVC affects the mortality and to analyze the factors that affect the mortality.

Materials and method

Patient characteristics

This study included all eligible patients diagnosed with acute leukemia from January 2010 to November 2020 who received remission induction chemotherapy with a non-tunneled CVC at Ajou University Hospital. All patients had Eastern Cooperative Oncology Group performance status of 0 or 1. Prophylactic antibiotics were prescribed for 197 patients (70.9%) comprising 163 patients (58.7%) of intravenous antibiotics according to a physician's discretion about underlying fever with suspicion of infection and 34 patients (12.2%) of oral antibiotics with fluoroquinolone, and antimicrobials were generally modified in case of persistence or occurrence of fever based on the Infectious Diseases Society of America (IDSA) guideline or the susceptibility test results of antimicrobials in the patients with a BSI [6]. Patients discharged from the hospital without fever and cases with long-term tunneled CVC (i.e., Hickman catheter) were excluded. Early removal of the CVC was performed because of CLABSI or at the physician's discretion in 47 patients according to the patients' clinical circumstances before culture results were confirmed. Multi-lumen CVC coated with silver sulfadiazine and chlorhexidine was inserted as anatomical accessibility of the patients by discretion of interventional radiologists of the institution with preference of subclavian vein followed by internal jugular vein. Dressing of the CVC was done once weekly with transparent film and 2% chlorhexidine alcohol-based solution, and surveillance was performed daily for early confirmation of involuntary displacement of CVC and exit site infection; furthermore, medical personnel were educated for aseptic manipulation of the CVC bundles with maximal efforts.

This research protocol was approved by the institutional review board (IRB) of Ajou University Hospital (IRB approval no. AJIRB-MED-MDB-21-014). Informed consent

was waived by the IRB because this study was conducted using the medical records of anonymized patients.

Clinical review

We retrospectively reviewed the patients for age, gender, body mass index (BMI), type of diagnosis, insertion site of the CVC, presence of underlying fever, presence of a BSI, peak C-reactive protein (CRP) level after neutropenic fever, duration of retention of the CVC, and the mortality.

Age was dichotomized into < 65 years or ≥ 65 years. The BMI was categorized as < 25 or ≥ 25 kg/m². The type of disease was classified as acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), mixed phenotype acute leukemia (MPAL), or acute promyelocytic leukemia (APL). The insertion site of the CVC was categorized as subclavian or jugular vein. Patients with a BSI were defined as those with clinical signs of infection and showing growth of microorganisms in at least one blood culture from a blood sample drawn from the peripheral blood or catheter hubs [12]. Underlying fever was defined as fever confirmed before or at the start date of chemotherapy. Fever was defined as a tympanic membrane temperature of 38° or higher [14], and the mortality was investigated in the period of hospital stay for the remission induction chemotherapy. In addition, subsequent BSI after decision for maintenance or early removal of the CVC was identified by retrospective clinical review for evaluation of the effect according to early removal of the CVC, classifying the patients with BSI or without BSI before the decision for maintenance or early removal of the CVC.

Statistical analysis

The chi-square test was used to compare the different groups for categorical variables. The binary logistic regression model was used to identify the factors affecting the mortality in univariate analysis and included factors for multivariate analysis with *p*-values less than 0.1 in univariate analysis. The chi-square test was conducted again to analyze the relationships between early removal or maintenance of the CVC and subsequent BSI. All statistical analyses were two-sided and were performed using IBM SPSS Statics software (version 25).

Results

Patient characteristics

Overall, 278 patients with neutropenic fever were identified, following insertion of a non-tunneled CVC in patients diagnosed with acute leukemia and receiving remission

induction chemotherapy. The CVC was removed early in 93 of these patients. The clinical characteristics of the patients are summarized in Table 1. Overall, 238 patients (85.6%) were < 65 years of age, with a median age of 51 years (15–77); 154 patients (55.4%) were male; and 192 patients (69.1%) had a BMI < 25 kg/m². The numbers of patients with AML, ALL/MPAL, and APL were 171 (61.5%), 69 (24.8%), and 38 (13.7%), respectively. A subclavian CVC was inserted in 232 patients (83.5%). Overall, 159 patients (57.2%) had underlying fever, and 95 patients (34.2%) had an accompanying BSI. The median peak CRP level was 17.8 mg/dl, and the median duration of CVC was 25 days. In addition, definite CRBSI was confirmed in one patient by positive culture results of CVC tip, peripheral blood, and blood drawn from the CVC.

The baseline patient characteristics showed a significantly higher BSI incidence ($p < 0.0001$) and significantly higher peak CRP levels ($p = 0.003$) in the early removal group. Median duration of retention of the CVC was 28 days for the maintenance group and 17 days for the early removal group, respectively.

The mortality according to the clinical characteristics

The in-hospital mortality for remission induction chemotherapy was identified in 33 patients (11.9%). Univariate and multivariate analyses of the mortality were performed, and the results are summarized in Table 2. The univariate analysis identified significant differences in gender (odds ratio (OR): 0.19, 95% confidence interval (CI): 0.07–0.51, $p = 0.001$), BSI (OR: 4.04, 95% CI: 1.89–8.65, $p < 0.0001$), and the peak CRP level (OR: 1.12, 95% CI: 1.08–1.17, $p < 0.0001$), while early removal of the CVC had no influence on the mortality (OR 1.16, 95% CI: 0.54–2.47, $p = 0.706$). Specifically, the mortality rate was 18.2% (28/154) for male patients and 4.0% (5/124) for female patients and, furthermore, 6.6% (12/183) for the patients without BSI and 22.1% (21/95) for the patients with BSI. In addition, the median peak CRP level was 15.8 mg/dl for the patients without mortality and 30.5 mg/dl for the patients with mortality. The mortality rate was 11.4% (21/185) for the patients with maintenance of the CVC and 12.9% (12/93) for the patients with early removal of the CVC, respectively.

Table 1 Patient characteristics

Clinical characteristics	Total ($n = 278$)	Maintenance ($n = 185$)	Early removal ($n = 93$)	p -value
Age				
< 65 years	238 (85.6%)	157 (84.9%)	81 (85.6%)	0.617
≥ 65 years	40 (14.4%)	28 (15.1%)	12 (14.4%)	
Gender				
Male	154 (55.4%)	99 (53.5%)	55 (59.1%)	0.373
Female	124 (44.6%)	86 (46.5%)	38 (40.9%)	
BMI				
< 25	192 (69.1%)	128 (69.2%)	64 (68.8%)	0.950
≥ 25	86 (30.9%)	57 (30.8%)	29 (31.2%)	
Diagnosis				
AML	171 (61.5%)	117 (63.2%)	54 (58.1%)	0.181
ALL/MPAL	69 (24.8%)	40 (21.6%)	29 (31.2%)	
APL	38 (13.7%)	28 (15.2%)	10 (10.8%)	
Insertion site of CVC				
Subclavian	232 (83.5%)	155 (83.8%)	77 (82.8%)	0.834
Jugular	46 (16.5%)	30 (16.2%)	16 (17.2%)	
Underlying fever				
No	119 (42.8%)	85 (45.9%)	34 (36.6%)	0.136
Yes	159 (57.2%)	100 (54.1%)	59 (63.4%)	
Bloodstream infection				
No	183 (65.8%)	144 (77.8%)	39 (41.9%)	< 0.0001
Yes	95 (34.2%)	41 (22.2%)	54 (58.1%)	
Median peak CRP level, mg/dl (95% CI)	17.8 (15.4–20.3)	14.5 (11.9–17.1)	23.3 (20.5–26.1)	0.003
Median duration of CVC, days (95% CI)	25 (23.7–26.3)	28 (27.3–28.7)	17 (14.6–19.4)	< 0.0001

BMI body mass index, *AML* acute myeloid leukemia, *ALL* acute lymphoblastic leukemia, *MPAL* mixed phenotype acute leukemia, *APL* acute promyelocytic leukemia, *CVC* central venous catheter, *CI* confidence interval, *CRP* C-reactive protein

Table 2 Univariate and multivariate analyses of mortality in acute leukemia patients with remission induction chemotherapy

Characteristics	Univariate			Multivariate		
	Odds ratio	95% CI	<i>p</i> -value	Odds ratio	95% CI	<i>p</i> -value
Age						
< 65 years	1		0.239			
≥ 65 years	1.73	0.70–4.30				
Gender						
Male	1		0.001	1		0.002
Female	0.19	0.07–0.51		0.19	0.06–0.54	
BMI						
< 25	1		0.203			
≥ 25	0.57	0.24–1.36				
Diagnosis						
AML	1					
ALL/MPAL	0.73	0.30–1.78	0.485			
APL	0.55	0.16–1.94	0.354			
Insertion site of CVC						
Subclavian	1		0.444			
Jugular	1.42	0.58–3.51				
Underlying fever						
No	1		0.244			
Yes	1.58	0.73–3.39				
Bloodstream infection						
No	1		< 0.0001	1		0.067
Yes	4.04	1.89–8.65		2.23	0.95–5.25	
Early removal of CVC						
No	1		0.706			
Yes	1.16	0.54–2.47				
Peak CRP level	1.12	1.08–1.17	< 0.0001	1.12	1.07–1.17	< 0.0001

HR hazard ratio, *CI* confidence interval, *BMI* body mass index, *AML* acute myeloid leukemia, *ALL* acute lymphoblastic leukemia, *MPAL* mixed phenotype acute leukemia, *APL* acute promyelocytic leukemia, *CVC* central venous catheter, *CRP* C-reactive protein

In multivariate analysis, the mortality was significantly lower in the female patients (OR: 0.19, 95% CI: 0.06–0.54, $p=0.002$) and correlated with the peak CRP level (OR: 1.12, 95% CI: 1.07–1.17, $p<0.0001$).

Incidence of subsequent BSI according to maintenance or early removal of the CVC

Incidence of subsequent BSI after clinical decision for maintenance or early removal of the CVC was rather higher in the patients with early removal of the CVC than the patients with maintenance of the CVC (early removal group, 22.6%, 21/93; maintenance group, 7.6%, 14/185, $p<0.0001$). Specifically, there was no significant difference for incidence of subsequent BSI in the patients without a BSI before the decision for early removal of CVC, while early removal group showed more frequent subsequent BSI in the patients with a BSI before the decision for early removal of CVC. (Table 3).

Discussion

Chemotherapy for patients with acute leukemia generally requires insertion of a CVC because of the frequent need for intravenous infusion of chemotherapeutic drugs, blood transfusions, and antibiotics. However, CRBSI is also a common problem in patients with acute leukemia. This study analyzed the factors affecting the in-hospital mortality and the effect of early removal of the CVC on the mortality during remission induction chemotherapy for acute leukemia in a single institution over a 10-year duration. The aim was to determine the clinical implications of decisions for early removal or maintenance of the CVC.

The mortality was identified more frequently in male patients with statistical significance. Early death rate was analyzed principally in the patients with APL because of characteristics of the disease in previous reports [15–17]. One report determined that male patients had a significantly higher proportion of early death in the patients [15],

Table 3 Subsequent blood stream infection incidence according to maintenance or early removal of central venous catheter

BSI before clinical decision for early removal of the CVC	Maintenance or early removal of CVC	Incidence of subsequent BSI	<i>p</i> -value
Total patients (<i>n</i> = 278)	Maintenance	7.6% (14/185)	< 0.0001
	Early removal	22.6% (21/93)	
Patients without BSI (<i>n</i> = 201)	Maintenance	7.1% (11/154)	0.141
	Early removal	14.9% (7/47)	
Patients with BSI (<i>n</i> = 77)	Maintenance	9.7% (3/31)	0.031
	Early removal	30.4% (14/46)	

CVC central venous catheter, BSI blood stream infection

while two reports analyzed that there were no significant relationship between gender and early mortality [16, 17]. In addition, there was a higher proportion of mortality rate in male AML patients with remission induction chemotherapy, though the statistical significance cannot be identified [18]. Male patients are considered to require greater caution on the mortality of remission induction chemotherapy, albeit clinical outcomes from a larger population would be needed.

The mortality was significantly related to the peak CRP level after neutropenic fever, as determined by both univariate and multivariate analyses. The CRP level was previously identified as a prognostic marker for patients with acute leukemia and neutropenic fever [19]. Previous studies have emphasized CRP monitoring for prognostic evaluation in hematologic malignancies [20, 21]; therefore, CRP monitoring is considered necessary in acute leukemia patients with neutropenic fever.

The focus of the present study was to determine whether a difference existed in the mortality in patients who underwent early removal of the CVC versus those who had the CVC maintained. The IDSA catheter-related infection guideline recommends removal of short-term CVCs, if a CRBSI is caused by gram-negative bacilli, *Staphylococcus aureus*, enterococci, fungi, or mycobacteria [12]. However, this guideline is unclear regarding the best strategies for patients with suspected catheter-related infection according to their clinical condition [22]. The concept of mucosal barrier injury laboratory-confirmed bloodstream infection (MBI-LCBI) was announced to distinguish from catheter-related infection [10]; however, the concept is limited in clinical circumstances because a lot of the patients determined as MBI-LCBI were the patients with CRBSI in the previous reports [9, 23, 24]. In addition, even though the Infectious Diseases Working Party of the German Society of Hematology and Medical Oncology announced the concepts of probable and possible CRBSI with strategies for CRBSI and updated recently [9, 25], further studies are needed for verification of clinical applicability about the recently updated guidelines. In this study, no difference was found for the mortality between the early CVC

removal and maintenance groups. In addition, a previous study on patients in an intensive care unit suggested that early removal of the CVC in patients with suspected catheter-related infections may not be necessary, because early removal of the CVC did not result in any difference in patient mortality. However, that study was limited because it excluded patients with hematologic malignancies [22]. In general, taken together, the findings of the present study and previous study that recommended the CVC maintenance until CVC is no longer needed support the maintenance of the CVC for as long as possible, provided that a CRBSI is not strongly suspected [26].

The findings of this study may have great significance as not only they are derived from practice conducted in the real world, but they support the idea that maintaining a CVC may not cause a difference in the mortality in acute leukemia patients undergoing remission induction chemotherapy unless CRBSI is strongly suspected.

In conclusion, early removal of the CVC had no benefit regarding the in-hospital mortality in patients with acute leukemia undergoing remission induction chemotherapy. Therefore, maintaining a CVC for as long as possible may be considered, if CRBSI is not strongly suspected.

Author contribution THK and JSP designed and planned the study. THK, YWC, MSA, YSC, HWL, SHJ, SYK, and JHC collected and analyzed clinical data. THK wrote the main manuscript, and THK and JSP edited the manuscript. THK, YWC, and JSP performed statistical analysis, and HYL reviewed the statistical analysis. All authors read and approved the final manuscript.

Data availability The datasets generated and/or analyzed during the current study are not publicly available due to the confidentiality of the data of patient but are available from the corresponding author on reasonable request.

Declarations

Ethics approval This study was conducted in accordance with the principles expressed in the Declaration of Helsinki. The study protocols were approved by the institutional review board of Ajou University Hospital (IRB approval no. AJIRB-MED-MDB-21-014).

Consent to participate The institutional review board of Ajou University Hospital decided to waive the informed consent for this study because it was a retrospective study using anonymized data.

Consent for publication Not applicable

Conflicts of interest The authors declare no competing interests.

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