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Master' s Thesis in
Medical Sciences

Can early removal of central venous
catheter influence duration of fever in
febrile neutropenic patients with
acute myeloid leukemia?

Ajou University Graduate School

Medical Sciences Major

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I submit this thesis as the
Master's thesis in Medical Sciences.

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ABSTRACT

Can early removal of central venous catheter influence duration of fever in febrile neutropenic patients with acute myeloid leukemia?

Neutropenia and fever precipitated from the state are very common and fatal problems to the patients with hematologic malignancy, especially acute leukemia. Additionally, febrile neutropenia costs a lot of money, because the patients generally need to be admitted to hospitals and treated by lots of medications like antibiotics and antifungal drugs. This study was designed to find out the factors that can decrease the duration of febrile neutropenia in acute myeloid leukemia patients and focused the impact due to early (i.e. less than 3 weeks) removal of the central venous catheter that inserted to most of acute myeloid leukemia patients receiving chemotherapy.

This retrospective study in a single center analyzed the effects of age, gender, body mass index(BMI), type of chemotherapy, presence of baseline fever before chemotherapy, presence of blood stream infection (BSI), insertion site of central venous catheter and early removal of central venous catheter on the duration of fever in acute myeloid leukemia patients with febrile neutropenia. The results were significant in both univariate and multivariate analyses depending on age, type of chemotherapy, presence of baseline fever and especially, early removal of central venous catheter (univariate analysis: $p=0.001$, multivariate analysis: hazard ratio 0.546, 95% confidence interval 0.368-0.810, $p=0.003$).

So, the physicians treating febrile neutropenic patients with acute myeloid leukemia may need to actively consider early removal of central venous catheter for reducing the duration of febrile neutropenia.

***Key Words:* Central venous catheter, Duration of fever, Neutropenia, Acute myeloid leukemia**

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I. INTRODUCTION

Neutropenia and its complications caused by systemic chemotherapy to cancer diseases have induced major dose-limiting toxicities to many cancer patients.(1) Especially, febrile neutropenia is regarded as a medical emergency by most of clinical physicians and generally prompts immediate hospitalization for fever focus evaluation and management like using empirical broad-spectrum antibiotics. In a retrospective study, mortality of febrile neutropenia in leukemia and lymphoma patients was 14.3% and 8.9%, mean length of stay in leukemia and lymphoma patients was 19.7 and 10.7 days, furthermore, mean costs of hospitalization in leukemia and lymphoma patients were 38,583 and 18,437 dollars.(2)

For this reason, many physicians and researchers have tried some attempts to reduce duration of febrile neutropenia. It is recommended that myeloid colony-stimulating factors should be used for the patients in whom the expected risk of neutropenic fever is $\geq 20\%$ to reduce the occurrence of the neutropenic fever by the Infectious Diseases Society of America (IDSA) guideline(3), because it was associated with reduction in febrile neutropenia and early deaths, including infection-related mortality in meta-analyses.(4) Furthermore, it is mentioned that fluoroquinolone prophylaxis be considered for high-risk patients who have very severe neutropenia with extended duration ($ANC \leq 100$ cells/ mm^3 for more than 7 days) for prevention of febrile neutropenia in the guideline.(3)

Patients with hematologic disorders frequently require the insertion of medium or long-term central venous catheters (CVCs) for stem-cell transplantation, the administration of chemotherapy, or transfusion of blood products.(5) We have already known that the CVC is a major source of bloodstream infections in the neutropenic patient populations in addition to the gastrointestinal tract.(3)

But, there have been no reports that covered whether early removal of CVC influences duration of febrile neutropenia in the cases except for those of catheter-related bloodstream infection (CRBSI). This study was designed to investigate the factors influencing the duration of febrile neutropenia including early removal of CVCs except for CRBSIs.

II. MATERIALS and METHODS

A. Study Population

In this retrospective study, a total of 102 patients were diagnosed as acute myeloid leukemia and treated with conventional chemotherapy at Ajou University Hospital between January 2009 and December 2014. In the courses of their chemotherapy cycles, a total of 269 CVC insertions were performed and 248 cases were accompanied with febrile neutropenia. Among those cases with febrile neutropenia, early CVC removals due to malfunction (11 cases) or other causes (23 cases) and 2 cases of early mortality due to non-infectious causes within 30 days after diagnosis were excluded. And cases with catheter-related bloodstream infection (CRBSI) (33 cases) were excluded. Finally, 179 CVC insertion cases with febrile neutropenia were eligible for analysis.

B. Variables of clinical characteristics and experimental definition

Clinical characteristics of cases were analyzed in terms of age, gender, body mass index (BMI), type of chemotherapy, duration of hospitalization, duration of central venous catheterization, duration of fever, presence of baseline fever, insertion site of CVC, presence of blood stream infection (BSI), execution of early removal of CVC. The data were collected from the medical records of Ajou University Hospital. Age was divided into less than 65 or ≥ 65 years. BMI was categorized as less than 25 or ≥ 25 kg/m². Type of chemotherapy was divided into remission induction, consolidation or salvage chemotherapy. Insertion site of CVC was categorized as subclavian vein or jugular vein. In addition, the microbiology results of all clinical specimens were collected. Fever was defined as a measurement of oral temperature not fewer than 38.3°C, or a temperature of $\geq 38^\circ\text{C}$ continued over a one-hour. Febrile neutropenia was defined as the outbreak of fever in a state of grade 4 neutropenia (ANC $< 0.5 \times 10^9/\text{L}$). (6-8) Catheter-related bloodstream infection (CRBSI) was defined as the same microorganism grown from at least one percutaneous blood culture and from a culture of the catheter tip (> 15 colony-forming units), or a growth of microbes from blood sample

drawn from a catheter hub at least 2 hours before microbial growth was detected in a blood sample obtained from a peripheral vein.(9) Patients with BSI were defined as those with clinical signs of infection and the microorganism grown from at least one percutaneous blood culture without detecting microorganism from a culture of the catheter tip or from blood sample drawn from a catheter hub. CVCs were removed based on the patients' conditions and circumstances by the physician's decisions. We defined the early removal of CVC as it had been maintained for less than 3 weeks (21 days).

C. Statistical analysis

The characteristics of study populations were compared and analyzed by the description for categorical variables. Duration of fever was estimated by the Kaplan–Meier method, and was compared by the Log Rank method. The Cox proportional hazard model was used in the multivariate analysis of prognostic factors. P values lower than 0.05 were considered statistically significant. Statistical analysis was performed using SPSS software version 20.0 (IBM, Armonk, NY, USA).

III. RESULTS

A. Characteristics of patients and central catheter insertion cases

In this retrospective study, a total of 102 patients were eligible for analysis and 179 CVC insertion cases with febrile neutropenia were finally analyzed. Baseline characteristics of total cases were described in Table 1. Median age of those patients was 51 (range 17-77) years old and 92 patients (51.4%) were male. 79 (44.1%), 77 (43.0%), and 23 (12.8%) cases were occurred during remission induction, consolidation, and salvage chemotherapy, respectively. Mean duration of hospitalization, catheterization and febrile neutropenia was 31.5 (range 16-49), 25.3 (range 8-39), and 7.9 (1-29) days, respectively. 29 (16.2%) cases had baseline fever before CVC insertion. Subclavian central venous catheterization was performed in 154 (86.0%) cases, on the other hand, jugular vein was used in 25 (14.0%) cases. BSI was detected in 49 (27.4 %) cases. In 40 (22.3 %) cases, CVC was removed before continuation of 3 weeks under physician's medical decision.

Table 1. Clinical characteristics of CVC insertion cases in acute myeloid leukemia patients with febrile neutropenia

| Clinical characteristics | N = 179 |
|---|-------------------|
| Median age, years (range) | 51 (17-77) |
| Gender (male:female) | 92:87 (51.4:48.6) |
| BMI (mean, range) | 24.5 (17.0-41.1) |
| Type of chemotherapy | |
| Remission induction CTx. | 79 (44.1%) |
| Consolidation CTx. | 77 (43.0%) |
| Salvage CTx. | 23 (12.8%) |
| Duration of hospitalization, days (mean, range) | 31.5 (16-49) |
| Duration of catheterization, days (mean, range) | 25.3 (8-39) |
| Duration of fever, days (mean, range) | 7.9 (1-29) |
| Presence of baseline fever | |
| Yes | 29 (16.2%) |
| No | 150 (83.8%) |
| Insertion site of CVC | |
| Subclavian vein | 154 (86.0%) |
| Jugular vein | 25 (14.0%) |
| Presence of BSI | |
| Yes | 49 (27.4%) |
| No | 130 (72.6%) |
| Early removal of CVC | |
| Yes | 40 (22.3%) |
| No | 139 (77.7%) |

BMI body mass index; CTx. chemotherapy

B. Duration of febrile neutropenia according to the clinical characteristics of central catheter insertion cases

Univariate and multivariate analyses about duration of fever were performed and the results are summarized in Table 2 and Table 3. In univariate analysis, mean duration of fever was statistically longer in cases of patients with older age (≥ 65 years old), remission induction and salvage chemotherapy rather than consolidation chemotherapy and with baseline fever. Especially, mean duration of fever in cases with early removal of CVC was 5.6 (95% CI, 4.6-6.6) days, which was statistically shorter than 8.0 days (95% CI, 7.5 -9.6) in cases without early removal of CVC ($p=0.001$, Table 2). However, the presence or absence of BSI and CVC insertion sites between jugular and subclavian vein did not show significant difference in the mean duration of fever.

In multivariate analysis, this trend was maintained. The duration of fever became longer in the patients with older age (≥ 65 years old, $p=0.011$, HR 1.738, 95% CI 1.135-2.661) and the fever was continued longer in non-consolidation chemotherapy which means remission induction chemotherapy or salvage chemotherapy than consolidation chemotherapy ($p=0.002$, HR 1.654, 95% CI 1.205-2.271). Additionally, presence of baseline fever was also significant ($p=0.011$, HR 1.797, 95% CI 1.142-2.830) and early removal of CVC significantly shortened the duration of fever which was consistent with the result of univariate analysis ($p=0.003$, HR 0.546, 95% CI 0.368-0.810).

Table 2. Univariate analysis of factors for duration of fever in acute myeloid leukemia patients with febrile neutropenia

| Characteristics (N=179) | Duration of fever, day (mean, 95% CI) | P value |
|----------------------------|---------------------------------------|------------------|
| Age | | |
| <65 (N=148) | 7.4 (6.5-8.3) | <u>0.03</u> |
| ≥65 (N=31) | 10.2 (7.8-12.6) | |
| Gender | | |
| Male | 7.8 (6.7-9.0) | 0.79 |
| Female | 7.9 (6.6-9.2) | |
| BMI | | |
| <25 (N=109) | 7.7 (6.6-8.8) | 0.60 |
| ≥25 (N=70) | 8.1 (6.6-9.6) | |
| Type of chemotherapy | | |
| Remission induction CTx. | 9.8 (8.5-11.1) | <u><0.001</u> |
| Consolidation CTx. | 5.4 (4.4-6.5) | |
| Salvage CTx. | 9.5 (6.6-12.4) | |
| Presence of baseline fever | | |
| No | 7.1 (6.3-8.0) | <u>0.001</u> |
| Yes | 11.7 (9.0-14.2) | |
| Presence of BSI | | |
| No | 8.0 (7.0-9.0) | 0.717 |
| BSI | 7.6 (5.9-9.2) | |
| Insertion site of CVC | | |
| Subclavian vein | 8.0 (7.1-9.0) | 0.318 |
| Jugular vein | 6.9 (4.9-8.8) | |
| Early removal of CVC | | |
| No | 8.0 (7.5-9.6) | <u>0.001</u> |
| Yes | 5.6 (4.6-6.6) | |

BMI body mass index; CTx. chemotherapy

Table 3. Multivariate analysis of factors for duration of fever in acute myeloid leukemia patients with febrile neutropenia

| Characteristics (N=179) | Hazard ratio | 95% CI | P value |
|----------------------------|--------------|-------------|--------------|
| Age | | | |
| <65 (N=148) | 1 | 1.135-2.661 | <u>0.011</u> |
| ≥65 (N=31) | 1.738 | | |
| Gender | | | |
| Male | 1 | 0.727-1.351 | 0.954 |
| Female | 0.991 | | |
| BMI | | | |
| <25 (N=109) | 1 | 0.792-1.472 | 0.628 |
| ≥25 (N=70) | 1.080 | | |
| Type of chemotherapy | | | |
| Consolidation CTx. | 1 | 1.205-2.271 | <u>0.002</u> |
| Non-consolidation CTx. | 1.654 | | |
| Presence of baseline fever | | | |
| No | 1 | 1.142-2.830 | <u>0.011</u> |
| Yes | 1.797 | | |
| Presence of BSI | | | |
| No | 1 | 0.807-1.660 | 0.428 |
| BSI | 1.157 | | |
| Insertion site of CVC | | | |
| Subclavian vein | 1 | 0.525-1.271 | 0.370 |
| Jugular vein | 0.817 | | |
| Early removal of CVC | | | |
| No | 1 | 0.368-0.810 | <u>0.003</u> |
| Yes | 0.546 | | |

BMI body mass index; CTx. chemotherapy

IV. DISCUSSION

Febrile neutropenia is an important issue in the clinical status managing the patients treated by the chemotherapeutic agents, especially, the patients with hematologic malignancy. This retrospective study was focused on the duration of fever in febrile neutropenic patients with acute myeloid leukemia and analyzed the factors that can influence the duration of fever in the patients.

First, older age (≥ 65 years) showed significantly longer duration of fever in the univariate and multivariate analyses. Klastersky J, et al. invented the multinational association for supportive care in cancer risk index: a multinational scoring system for identifying low-risk febrile neutropenic cancer patients and younger age (< 60 years) was associated with low risk of febrile neutropenia.(10) Additionally, Crawford J, et al. thought that age itself was general risk factor for the development of severe neutropenia or febrile neutropenia.(11) Although the reports didn't mention about duration of fever, the results of this study have something in common with the results of those reports.

There were some previous reports about incidence of infectious complications according to gender and BMI and the reports detected the infectious complications were not related to gender or BMI.(12, 13) Result of this study about gender and BMI had something in common with the reports in the univariate and multivariate analyses.

Induction and salvage chemotherapy are generally performed by more amounts of chemotherapeutic drugs, of course, those provoke longer duration of febrile neutropenia generally and it was shown by a previous report.(14) This study also showed similar trend with the result.

Presence of baseline fever was significant in the both univariate and multivariate analyses. But there was a previous report that mentioned prognostic factors in the acute leukemia patients with chemotherapy and the results in the death and survival groups with acute leukemia were not significantly different as whether with or without episode of fever before chemotherapy.(15) There have been few reports about the relationship between baseline fever and the duration of fever in febrile neutropenic patients. Maybe, more researches will be needed for confirmation of the relationship between baseline fever and the duration of fever

in febrile neutropenic patients with acute myeloid leukemia.

There was a study about blood stream infection and duration of fever for the period of chemotherapy-induced neutropenia in adult patients with acute myeloid leukemia according to the chemotherapy cycles. In the result, first chemotherapeutic cycle had lower incidence of BSIs, but duration of fever was higher than second, third or fourth cycles of chemotherapy. We can infer indirectly that duration of fever is not related with the presence of BSI from this result and our study data showed the duration of fever was not associated with BSI significantly in the both univariate and multivariate analyses.(16)

Insertion site of CVC did not influence the duration of fever significantly in both univariate and multivariate analyses in this study. It is known that CRBSI is provoked more frequently in the case of jugular access than that of subclavian access.(17) But, the result of investigation about the duration of fever according to the insertion site of CVC is insufficient, especially in the patients with the febrile neutropenic patients with acute myeloid leukemia. Duration of fever was not associated with the insertion site of CVC in this study.

There were some reports about the relationship between removal of CVC and bacteremia or fungemia(18, 19) and the IDSA guideline recommended that CRBSI caused by the bacteria like *Staphylococcus aureus*, *Pseudomonas aeruginosa*, fungi, or mycobacteria, catheter removal is recommended in addition to systemic antimicrobial therapy, whereas, the CRBSI caused by coagulase-negative staphylococci, the catheter may be retained using systemic therapy with or without antibiotic lock therapy.(3) But there were no reports about the relationship between early removal of CVC and duration of fever in febrile neutropenic patients with acute myeloid leukemia. Both univariate and multivariate analyses showed early removal of CVC could reduce duration of fever significantly in this study.

There are some limitations of this study. This is retrospective study and has limited number of populations in a single center. Furthermore, this study was performed only in AML patients, so the result of study can be altered in other disease populations such as lymphoproliferative disorders. Further researches may be needed for verification of benefits of early removal of CVCs in hematologic disease patients receiving chemotherapy.

In conclusion, early removal of CVCs can reduce the duration of fever in febrile neutropenic patients with acute myeloid leukemia. So, physicians treating AML patients by

chemotherapy should think about the ways to reduce the duration of maintenance of CVCs.



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급성 골수성 백혈병으로 항암화학치료중 발생한 호중구 감소 발열 환자에서 중심 정맥관의 조기 제거가 발열의 기간에 영향을 미칠 수 있는가?

아주대학교 대학원 의학과

김태환

(지도교수: 박준성)

호중구 감소와 그로 인해 발생하는 발열은 혈액암, 특히 급성 백혈병을 가진 환자에게 매우 흔히 발생하며 치명적인 문제이다. 또한, 일반적으로 호중구 감소 발열 환자들은 병원에 입원하여 항생제와 항진균제 같은 여러 약물들로 치료가 이루어지기에 많은 비용 또한 수반한다. 본 연구는 급성 골수성 백혈병 환자군에서 호중구 감소 발열의 기간을 줄일 수 있는 요인을 밝혀내고자 하였으며 특히 대부분의 항암화학치료를 받는 급성 골수성 백혈병 환자들에게 삽입되는 중심 정맥관의 조기 제거(3주 이내)의 영향에 초점을 맞추었다.

이 연구는 단일 의료기관에서 시행된 후향적 연구로 호중구 감소 발열을 동반한 급성 골수성 백혈병 환자에서 나이, 성별, 체질량지수(BMI), 항암화학치료의 종류, 항암화학치료 전 기저 발열의 유무, 혈류 감염의 유무, 중심 정맥관 삽입 부위, 중심 정맥관의 조기 제거 여부에 따라 발열의 기간에 어떠한 영향을 미치는지 분석하였다. 결과는 나이, 항암화학치료의 종류, 기저 발열의 유무 그리고 특히, 중심 정맥관의 조기 제거 여부에 따라 일변량 분석과 다변량 분석 모두에서 유의한 결과를 보였다. (일변량 분석: $p=0.001$, 다변량 분석: 위험 비율 0.546, 95% 신뢰 구간 0.368-0.810, $p=0.003$).

그러므로 급성 골수성 백혈병 환자의 호중구 감소 발열을 치료하는 의사는 호중구 감소 발열의 기간을 단축시키기 위해 중심 정맥관의 조기 제거를 적극적으로 고려하는 것이 필요할 것이다.

핵심어: 중심 정맥관, 발열의 기간, 호중구 감소, 급성 골수성 백혈병

