

Prospective Randomized Comparative Observations of Infectious Complications with or without Antimicrobial Prophylaxis, during Autologous Stem Cell Transplantation

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Background: A prospective randomized comparative observation was performed to assess the benefit of prophylactic antimicrobials in autologous stem cell transplantation (ASCT).

Methods: Forty consecutive patients, with multiple myelomas (MM, 28 patients) or a non-Hodgkin's lymphoma (NHL, 12 patients), were stratified by disease and randomly allocated to receive (prophylaxis group, 21 patients) or not receive (control group, 19 patients) prophylactic antimicrobials. The prophylactic antimicrobials consisted of ciprofloxacin (500mg twice daily p.o.), fluconazole (100mg twice daily p.o.) and acyclovir (400mg every 8 h p.o.), starting 1 day before high-dose chemotherapy (high-dose melphalan for MM and BEAM for NHL), and continuing until neutrophil engraftment or the occurrence of infection.

Results: At least one episode of fever occurred in 15 of the 19 (79%) patients in the control group, compared with 12 of the 21 (57%) in the prophylaxis group ($P=NS$). Microbiologically or clinically documented infections occurred in 4 patients (21%) in the control group, but none occurred in the prophylaxis group ($P=NS$). The documented infections in the control group included 3 staphylococcal bacteremias and 1 herpes skin infection. No deaths, invasive fungal infections or serious adverse events occurred in either group. The median duration of fever (9 days in the control group and 11 days in the prophylaxis group), therapeutic antimicrobial therapy (9 days in the control group and 11 days in the prophylaxis group) and hospital stay after ASCT (19 days in both groups) did not differ between the groups.

Conclusion: This small-sized prospective randomized comparative observation showed no beneficial effects of antimicrobial prophylaxis in ASCT. (*Korean J Hematol 2006;41:282-288.*)

Key Words: Autologous stem cell transplantation, Infectious complications, Antimicrobial prophylaxis

INTRODUCTION

High-dose chemotherapy accompanying autologous stem cell transplantation (ASCT) has been reported to significantly improve response and

survival rates in both hematologic malignancies and solid tumors.¹⁾ Despite the impressive array of antimicrobial agents, however, infection continues to be a major cause of morbidity and mortality following hematopoietic stem cell transplantation.²⁾ Prophylactic antimicrobials, in most

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cases a quinolone, an azole or amphotericin B and an anti-herpetic antiviral agent, have therefore been frequently used to reduce the risk of infection.³⁾ Effective prophylaxis against specific infections has allowed the administration of increasingly potent conditioning regimens, thereby prolonging survival in hematopoietic stem cell transplantation recipients.⁴⁾

Although the prophylactic administration of antimicrobials has been shown to benefit patients undergoing allogeneic stem cell transplantation (alloSCT), its benefits in ASCT are not clear. In contrast to alloSCT, ASCT causes a relatively short period of neutropenia,^{5,6)} thus decreasing the risk of infection. Although a survey report showed that prophylactic antimicrobials have been used frequently for ASCT,⁷⁾ the benefits of antifungal and antiviral prophylaxis have not been confirmed. In neutropenic patients, antibacterial chemoprophylaxis with fluoroquinolones has reduced the incidence of Gram negative bacteremia.⁸⁾ However, the emergence of fluoroquinolone-resistant Gram negative bacilli and the increased incidence of *Viridans streptococci* bacteremia is of increasing concern.^{9,10)} A recent prospective, single arm study reported that infectious morbidity during ASCT was low in patients not receiving prophylactic antimicrobials.¹¹⁾ To our knowledge, there have been no prospective randomized comparison trials studying the beneficial effects of prophylactic antimicrobials during ASCT. We therefore performed a prospective randomized comparative observation to assess the benefit of prophylactic antimicrobials in ASCT.

MATERIALS AND METHODS

1. Patients

Between January 2004 and June 2005, 40 consecutive patients with multiple myeloma (MM, 28 patients) or non-Hodgkin's lymphoma (NHL, 12 patients) undergoing ASCT in the Asan Medical Center were enrolled in this study. Each patient was 15~70 years old had an ECOG per-

formance status of 0~2; was infused with over 3×10^6 CD34+ cells/kg; had adequate cardiac, pulmonary, hepatic, renal and hematopoietic function; did not have an active infection; and had not received antimicrobial therapies for at least 7 days. Patients with human immunodeficiency virus or human T-lymphotrophic virus-1 associated malignancies, malignancies involving the central nervous system, or a history of other malignant disease within the previous 5 years were excluded. Upon admission and prior to high-dose chemotherapy, each patient signed the appropriate informed consent documents. All protocols were approved by the Institutional Review Board of the Asan Medical Center.

2. Antimicrobial prophylaxis, high-dose chemotherapy and supportive care

After being stratified by disease, the patients were prospectively randomized to receive (prophylaxis group) or not receive (control group) antimicrobial prophylaxis. Patients were cared for in a single room, with reverse isolation strictly maintained to prevent infectious complications. Prophylactic antimicrobials consisted of domly allocated into apyylactic lacticiproflaxacin (500 mg twice daily p.o.), fluconazole (100mg twice daily p.o.) and acyclovir (400mg every 8 h p.o.), started 1 day prior to initiation of high-dose chemotherapy and stopped when the absolute neutrophil count¹⁾ reached $500/\text{mm}^3$ after nadir or infection occurred.

High-dose chemotherapy regimens consisted of high-dose melphalan for patients with MM¹²⁾ and BEAM (carmustine, etoposide, cytarabine, and melphalan) for patients with NHL.¹³⁾ Mobilized autologous peripheral blood stem cells were infused on day 0. G-CSF (Neutrogen[®], Choongwae Pharma Corp., Seoul, Korea) $5 \mu\text{g}/\text{kg}/\text{day}$ was begun on day 1 of stem cell infusion and continued until ANC reached $1,000/\text{mm}^3$ or higher on 2 consecutive days.

Patients received transfusions of red blood cells and platelets as clinically indicated. Gener-

ally, platelets were single-donor transfusions, administered to keep platelet counts above 20,000/mm³ or for clinical bleeding.

3. Diagnosis of infection and antimicrobial therapy

Fever was defined as a single oral temperature of $\geq 38.3^{\circ}\text{C}$ or a temperature of $\geq 38.0^{\circ}\text{C}$ for ≥ 1 hour according to the Infectious Diseases Society of America (IDSA) 2002 guidelines.¹⁴⁾ During each episode of fever, the causative pathogen was intensively searched by repeated cultures of blood, urine, sputum, feces, and any clinically suspicious secretions. The initial empiric antibiotics for the first episode of fever were ceftazidime and amikacin plus vancomycin. Vancomycin was introduced in the initial empiric antibiotics because every patient had central venous catheter. The decision of antibiotic regimen during the first week of therapy and duration of antimicrobial therapy were based on the IDSA 2002 guidelines.¹⁴⁾ Patients were followed at least until day 100 of ASCT to assess the infectious complications.

4. Statistical methods

Because of apparent limitations in accrual of sufficient patients for phase III study, this prospective comparative observation was designed and performed in randomized phase II fashion. Previous survey of our center showed around 85% of febrile episodes in patients undergoing ASCT. Assuming 10% difference of febrile episodes between prophylaxis and control group would be significant, 20 patients per treatment group were necessary for correct selection with 85% probability.¹⁵⁾ We planned to recruit total 40 patients for this trial. Randomization was performed with computer-generated random digit.

Patient characteristics and cell counts reported as medians and ranges were compared using the Mann-Whitney test, whereas proportions were compared using the χ^2 test. Time variables were calculated with the Kaplan-Meier method. All re-

ported *P*-values are two-sided, and *P*-values < 0.05 were considered significant. Statistical analysis was performed using SPSS for Windows V.12.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

1. Patient characteristics

Forty patients were randomized, 21 to the prophylaxis group and 19 to the control group. The two groups were well balanced for age, gender, underlying disease, disease status and dose of infused CD34+ cells (Table 1).

2. Infectious complications

Overall clinical courses and infectious complications are shown in Table 2. Nine patients (43%) in the prophylaxis group and 4 (21%) in the control group experienced no febrile episodes, whereas 11 patients (52%) in the prophylaxis group and 13 (68%) in the control group experienced one febrile episode. One patient (5%) in the prophylaxis group and 2 (11%) in the control group experienced 2 episodes of fever. These

Table 1. Patient characteristics

Characteristic	Prophylaxis group (n=21)	Control group (n=19)	<i>P</i>
Age (years)*	54 (15~66)	51 (38~65)	NS
Gender			
Male	12 (57%)	15 (79%)	NS
Female	9 (43%)	4 (21%)	
Disease			
Non-Hodgkin's lymphoma	6 (29%)	6 (32%)	NS
Multiple myeloma	15 (71%)	13 (68%)	
Status of disease			
1st CR	4 (19%)	2 (11%)	NS
≥ 2 nd CR	3 (14%)	1 (5%)	
Not in CR	14 (67%)	16 (84%)	
CD34+ cell dose ($\times 10^6/\text{kg}$)*	8.78 (3.21~35.08)	9.59 (4.32~38.90)	NS

*Data are reported as median (range).

Abbreviation: NS, not significant; CR, complete remission.

Table 2. Infectious complications and clinical courses

	Prophylaxis group (n=21)	Control group (n=19)	P
No. of febrile episodes during admission			
0	9 (43%)	4 (21%)	NS
1	11 (52%)	13 (68%)	
2	1 (5%)	2 (11%)	
Onset of 1st febrile episode*	Day+5 (day-4 to day+8)	Day+4 (day-8 to day+8)	NS
Duration of fever, days*	11 (0~39)	9 (0~17)	NS
Days of antibiotics, days*	11 (0~45)	9 (0~26)	NS
Classification of febrile episode			
Fever only	12 (57%)	11 (58%)	NS
Clinically documented	0	1 (5%)	
Microbiologically documented	0	3 (16%)	
Median days to ANC $\geq 500/\text{mm}^3$	10 (95% CI: 9~11)	10 (95% CI: 10~10)	NS
Median days to PLT $\geq 20,000/\text{mm}^3$	12 (95% CI: 11~13)	11 (95% CI: 10~12)	NS
Duration of admission, days*	19 (11~150)	19 (11~37)	NS

*Data are reported as median (range).

Abbreviation: NS, not significant; ANC, absolute neutrophil count; PLT, platelet.

Table 3. The 4 microbiologically or clinically documented infections in the control group

Pathogen	Infectious manifestation
Methicillin-sensitive <i>Staphylococcus aureus</i>	Bacteremia
Methicillin-sensitive <i>Staphylococcus epidermidis</i>	Bacteremia
Methicillin-resistant coagulase-negative <i>Staphylococcus</i>	Bacteremia
Herpes simplex	Herpes labialis

differences between groups were not statistically significant.

The onset of the first febrile episode was similar in the two groups: on median day +5 (range, day -4 to day +8) of ASCT in the prophylaxis group and on median day +4 (range, day -8 to day +8) in the control group. The median duration of fever was 11 days (range, 0~39 days) in the prophylaxis group and 9 days (range, 0~17 days) in the control group with no difference between the groups. The median number of days on antibiotics, 11 days (range, 0~39 days) in the prophylaxis group and 9 days (range, 0~26 days) in

the control group, also did not differ significantly. In the prophylaxis group, all febrile episodes consisted of fever only, with no clinically or microbiologically documented infections. Among the 15 febrile episodes in the control group, there were 1 clinically documented and 3 microbiologically documented infections. This classification of febrile episodes did not differ significantly between the groups.

There were also no statistically significant differences in median days to neutrophil and platelet engraftment. Absolute neutrophil count reached $500/\text{mm}^3$ or higher on median day 10 (95% CI: day 9~11) in the prophylaxis group and on day 10 (95% CI: day 10~10) in the control group. Platelet counts reached $20,000/\text{mm}^3$ or higher on median day 12 (95% CI: day 11~13) in the prophylaxis group and on day 11 (95% CI: day 10~12) in the control group. The duration of admission for ASCT did not differ between the groups it was a median of 19 days (range, 11~150 days) in the prophylaxis group and 19 days (range, 11~37 days) in the control group.

Table 3 shows the nature of the microbiologically and clinically documented infections, all

of which occurred in the control group. There were 3 incidents of *Staphylococcus* bacteremia: 1 methicillin-sensitive *S. aureus*, 1 methicillin-sensitive *S. epidermidis*, and 1 methicillin-resistant coagulase-negative *Staphylococcus*. There was also a clinically documented infection with herpes labialis. There were no incidents of invasive fungal infection or systemic viral infection in either group. No serious adverse events or infection-related mortality occurred during the study period.

DISCUSSION

We have shown here that antimicrobial prophylaxis was not effective in preventing infectious complications during ASCT. A prospective study of patients receiving ASCT without prophylactic antimicrobial prophylaxis reported that the infectious morbidity during ASCT was low even in patients with heavily pretreated hematological malignancies.¹¹⁾ In that study, all 23 patients had at least one episode of fever during ASCT, with most of these fevers being of unknown origin. It was reported that clinically or microbiologically documented infections occurred in only five patients (21.7%). These included bacteremias (three patients), perianal abscess (one patient), and catheter-related phlebitis (one patient). They reported that no deaths, invasive fungal infections, or serious adverse events occurred. The median duration of fever, intravenous antimicrobial therapy, and hospital stay after transplantation were comparable to their historical controls. These findings indicated that infectious morbidity during ASCT without prophylactic antimicrobials was low, even in patients with heavily pretreated hematological malignancies. However, these results also suggested that further randomized trials would be needed to clarify the cost benefits of prophylactic antimicrobials in ASCT and to determine the most appropriate use of antimicrobials in patients receiving ASCT.

Although the benefits of prophylactic anti-

microbials in ASCT are not clear, the common practice is to use these treatments, with the most frequent regimens being a quinolone plus an azole or amphotericin B.^{16,17)} A comparison study found that omission of prophylactic antimicrobials might not jeopardize patient health and survival,¹³⁾ but, in that study, the population was unbalanced. All patients not receiving prophylactic antimicrobials had sarcomas and received only myelosuppressive chemotherapy, whereas patients receiving prophylactic antimicrobials had myeloma, lymphoma, or breast cancer, and all received myeloablative high-dose chemotherapy.

Current study was performed as a prospective randomized comparison of infection-related outcomes after ASCT with or without using prophylactic antimicrobials. Our results are in agreement with those from the previous single-arm observational study, suggesting that prophylactic antimicrobials are not beneficial for patients undergoing ASCT.^{3,11)} We observed no incidents of invasive fungal infection or systemic viral illness, suggesting that anti-fungal and anti-viral agents could be omitted from patients undergoing ASCT. We observed one viral illness, a superficial skin infection, and 3 Gram (+) bacteremias in the control group, but their incidence did not differ significantly from that of the prophylaxis group. Because all bacteremias were of Gram (+) organisms, the role of ciprofloxacin prophylaxis could not be assessed.

Although our findings indicate that the regimen of antimicrobial prophylaxis described here had no role in preventing infectious complications during ASCT, we cannot conclude that antimicrobial prophylaxis is ineffective in preventing infections during ASCT. Rather, our results more narrowly indicate that the drug regimens used in this study were not effective in diminishing the infectious complications of ASCT. Ciprofloxacin had been used for antibacterial prophylaxis during ASCT in our institution till the initiation of this trial. And we used ciprofloxacin rather than levofloxacin for current study, be-

cause there was no strong recommendation or evidence favoring the use of prophylactic use of levofloxacin at the beginning of current study. New and more efficient combinations of antimicrobial prophylaxis may improve the clinical course of ASCT.

After completion of current study, there have been reports that prophylactic treatment with levofloxacin is an effective and well-tolerated way of preventing febrile episodes and other relevant infection-related outcomes in patients with cancer and profound and protracted neutropenia.¹⁸⁻²⁰⁾ These reports have provided evidence of the significant benefit of levofloxacin prophylaxis, but there is an opinion that the price of this benefit may be high.²¹⁾ Levofloxacin prophylaxis also has general limitations that all antibiotic interventions come at a price, including increased costs, side effects, susceptibility to enteric infections, and emergence of resistant endogenous organisms. And the study populations were not homogeneous in the aspect of disease and setting of disease status.

The patient care setting of our institution might also be different from that of western countries. Not only every patient of current study but also all patients undergoing ASCT in Korea are admitted to the hospital from the first day of conditioning high-dose chemotherapy. When a patient is cared as out-patient setting for ASCT procedure, it is extremely difficult to admit the patient for unexpected and urgent in-patient care in Seoul, Korea. This is because of room availability in general Korean tertiary hospital. Therefore patients are admitted and cared as in-patient setting for whole procedure of ASCT in our institution. This discrepancy of patient care policy might affect the efficacy of antimicrobial prophylaxis during ASCT.

A proper assessment of the role of antimicrobial prophylaxis during ASCT requires the performance of phase III randomized comparison study. However, the feasibility of conducting such study with tertiary university hospitals in

Korea is complicated by the fact that these institutions differ in conditioning regimen, policy of antimicrobial prophylaxis, and detailed supportive care. This institutional variance led us to design a single-center prospective study with a limited number of patients. Although our institution is one of the largest referral centers in Korea, the number of patients we were able to recruit was insufficient for a randomized phase III comparative study. Despite the study we performed was a phase II trial, it could still provide important results.

In conclusion, this small-sized prospective randomized comparative observation showed that antimicrobial prophylaxis with ciprofloxacin, fluconazole and acyclovir had no beneficial effects in preventing infectious morbidity during ASCT.

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요 약

배경: 자가 조혈모세포이식술 후 예방적 항균제의 유효성 평가를 위해 전향적 무작위 비교 관찰을 하였다.

방법: 40명(비호지킨 림프종 12명, 다발골수종 20명)을 진단에 따라 총화 후 예방적 항균제 투여 군(21명)과 대조군(19명)으로 무작위 배치하였다. 예방적 항균제 투여군은 씨프로플록사신 경구 500mg 매일 2회, 플루코나졸 경구 100mg 매일 2회, 아씨클로비아 경구 400mg 매 8시간 투여 받았다. 이는 고용량 화학 요법 시행 1일 전부터 시작하여 호중구 생착 혹은 감염증 발생 때까지 계속하였다.

결과: 대조군의 79% (15/19), 그리고 예방군 57% (12/21)에서 최소 1회 이상의 발열이 발생하여 통계적 차이는 없었다. 미생물학적 또는 임상적으로 증명된 감염증은 대조군에서 4명(21%) 발생하였고 예방군에서는 없었으나 통계학적 차이는 없었다. 양

군 모두 사망, 침습적 진균증, 심각한 부작용 등은 없었다. 발열 기간, 치료적 항생제 투여 기간, 입원 기간도 차이가 없었다.

결론: 비록 소규모이지만 이 전향적 무작위 비교 관찰 결과, 이 연구에 동원된 용법 및 용량의 예방적 항균제 사용은 자가조혈모세포이식술 후 감염증 예방에 도움이 되지 않았다.

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