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Febrile neutropenia in allogeneic and autologous peripheral blood stem cell transplantation and conventional chemotherapy for malignancies

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Summary:

The risk and outcome of infection in febrile neutropenic patients is mainly determined by the duration of neutropenia, the underlying disease or the treatment. This study was undertaken to compare infections and the outcome after conventional chemotherapy (CCT), allogeneic PBSC transplantation (alloPBSCT) or autologous PBSC transplantation (autoPBSCT), during the period of neutropenia, in a single center. A total of 145 patients (50 in CCT group, 50 in alloPBSCT and 45 in autoPBSCT) were evaluated. In the alloPBSCT group, 86% of the patients (43/50), in the autoPBSCT group 93% of the patients (42/45) and in the CCT group 92% (46/50) of the patients had at least one febrile episode during their neutropenic period ($P > 0.05$). Microbiologically and/or clinically documented infection rates were 50% (25/50), 42% (19/45) and 48% (24/50) respectively. Gram-positive pathogens, mostly coagulase-negative staphylococci were the most frequent cause of bacteremias in all groups. The frequency of CNS infections was significantly higher in the alloPBSCT and autoPBSCT groups compared to the CCT group ($P < 0.008$ and $P < 0.04$, respectively). Catheter infections were frequent in the PBSCT groups and pulmonary infections were more frequent in the CCT group ($P < 0.05$). The CCT group needed longer antibiotic usage compared to the alloPBSCT group ($P < 0.006$). The duration of neutropenia and the type of treatment given, does not affect the rate of febrile episodes, but affects the type of infections in febrile neutropenic patients. *Bone Marrow Transplantation* (2000) **26,** 211–214.

Keywords: febrile neutropenia; allogeneic peripheral blood stem cell transplantation; autologous peripheral blood stem cell transplantation; chemotherapy

Infectious complications are associated with morbidity and mortality in patients with malignancies. Currently, this complication occurs more frequently and is related to the increased use of high-dose treatment modalities, and stem cell transplantation. A variety of factors contribute to the pathogenesis of infection in these patients. Although direct damage to the skin and mucosal barriers and defects in cellular and humoral defense mechanisms are important factors, the severity and duration of neutropenia is the main determinant in developing infectious complications.[1] The risk and outcome of infection in patients with febrile neutropenia is mainly determined by the duration of neutropenia and the underlying disease.[2] It is common to see most of these disorders simultaneously occurring in a single patient.

All these factors are the result of either the underlying disease or the treatment given to the patient, and in most of the cases, the treatment is the main determinant of the type and severity of infection, regardless of the underlying disease.

This study was designed to compare the differences in infections and the outcomes related to three different treatments (conventional chemotherapy (CCT), allogeneic peripheral blood stem cell transplantation (alloPBSCT) and autologous peripheral blood stem cell transplantation (autoPBSCT)) during the period of neutropenia in a single center between 1997 and 1999.

Materials and methods

Procedures

In Ankara University, Medical Faculty, Hematology Department, a total of 145 patients (50 in the CCT group, 50 in the alloPBSCT and 45 in the autoPBSCT) were evaluated to observe the differences in the periods of neutropenia between 1997 and 1999. The characteristics of the patients are shown in Table 1. The patients in the CCT group were cared for in rooms with three to six beds, with ordinary precautions against infection such as hand washing. The patients in the autoPBSCT group were cared for in single-nurse, single-bed rooms. Masks and gowns were routinely used. If a patient who underwent autoPBSCT experienced severe and prolonged neutropenia they were transferred to the special care unit until the resolution of neutropenia.

All patients who underwent alloPBSCT were cared for in the special BMT unit with reverse isolation, UV lamps, and a single nurse.

All patients who received allo and autoPBSCT received Hickmann catheters; the patients in the CCT group had catheters when appropriate.

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Table 1 Clinical characteristics of patients

	AlloPBSCT	*AutoPBSCT*	*Chemotherapy*
No	50	45	50
Age, median (range)	32.0 (14–47)	33.0 (15–59)	32.5 (16–59)
Sex			
Male	28	22	24
Female	22	23	26
Diagnosis			
AML	22	11	46
ALL	4	0	4
CML	21	0	
MDS	1	0	
Aplastic anemia	1	0	
Multiple myeloma	1	2	
Breast cancer		9	
Ovarian cancer		2	
Testicular cancer		1	
Hodgkin's disease		7	
Non-Hodgkin's lymphoma		11	
Lung cancer		2	
Treatment			
Bu + CY	49	23	
TBI + CY	1		
Melphalan, thiotepa, carboplatin		21	
Melphalan		1	
Ara-C, idarubicin			46
Vincristine, prednisolone, L-asparginase, Cy			4
Stem cell support 10^6 CD34-positive cells/kg	6.12 (0.53–20.64)	8.68 (1.70–33.20)	

Prophylaxis

Only the patients who underwent allo and autoPBSCT received prophylaxis. In the alloPBSCT group, fluconazole 200 mg/day and acyclovir 1 g/day were administered from days −8 to +180. Ciprofloxacin 400 mg/day was given from day −8 untill neutrophil engraftment and trimethoprim/sulphometaxazole from day −8 to day 0. In the autoPBSCT group, the same prophylaxis, with the exception of TMP/SMX, was used. The CCT group did not receive any prophylaxis.

Growth factors

All patients who underwent PBSCT received G-CSF at a dose of 5 μg/kg/day, starting from 24 h after the stem cell transplantation procedure and until the neutrophil count was above 1.0×10^9/l for 3 consecutive days; the first day was accepted as the day of neutrophil engraftment.

Microbiological investigations

Appropriate clinical examinations were performed once daily and body temperature was measured at least three times a day. Routine cultures from stools, urine and the mouth were examined twice weekly for contaminating pathogens in the PBSCT patients. If the body temperature of the patient was over 38°C, two blood cultures and catheter cultures were drawn at least once daily in both groups. In febrile patients, a thorough physical examination and chest X-ray was done.

Treatment

All patients received i.v. antibiotics if body temperature was above 38.5°C or was over 38°C twice separated by 12 h. Empirical antibiotics were administered according to the published EORTC recommendations.[3] A beta-lactam (cefepim 1 g three times a day or ceftazidime 2 g three times a day) or karbapenem (imipenem/cilastatin 500 mg four times a day or meropenem 1 g three times a day) and aminoglycoside (amikacin 1 g/day) was administered initially and, in patients who did not respond, a glycopeptide was added in the 72nd hour if the patient had a catheter or a suspicion of Gram-positive infection. If fever continued after 5 days, amphotericin-B was added. All patients with fever in the 72nd hour in the PBSCT group received a glycopeptide as they all had catheters. If patients had no fever for 4 consecutive days, all antibiotics were withdrawn.

Statistical analysis

For the analysis of the data, *t*-test, one way ANOVA and chi-square test were used.

Results

The overall results are summarized in Tables 2 and 3.

Neutropenia

The median duration of neutropenia was 12 (5–27), 11 (5–66) and 18 (8–30) days in the alloPBSCT, autoPBSCT and

Table 2 Clinical and microbiological characteristics of febrile episodes

	AlloPBSCT	*AutoPBSCT*	*Chemotherapy*	*P value*
Neutropenic days, median (range)	12 (5–27)	11 (5–66)	18 (8–30)[a]	0.001[a]
Febrile neutropenic days, median (range)	2 (0–12)	2 (0–9)	3 (0–12)	0.17
Days with neutropenia, median (range)	3 (0–10)	3.5 (0–20)	5 (0–10)	0.14
Clinical and microbiological infection	25 (50%)	19 (42%)	24 (48%)	0.25
Fever of unknown origin	18 (36%)	23 (51%)	24 (44%)	0.25
No infection	7 (14%)	3 (7%)	4 (8%)	0.25
Gram-negative infection	5 (10%)	5 (11%)	4 (8%)	0.25
Gram-positive infection	20 (40%)	9 (20%)	4 (8%)	0.005[a]
Coagulase-negative staphylococci	13	5	1	0.025[a]
Pneumonia	0 (0%)	2 (4%)	12 (24%)	0.008[a], 0.04[b], 0.005[c]
Days on antibiotics				
Median (range)	8 (0–25)	9 (0–30)	10.5 (0–28)	0.006[a]
Antibiotics combination				
Beta-lactam	2	3	3	
Beta-lactam/aminoglycoside	16	14	20	
Beta-lactam/aminoglycoside/glycopeptide	25	25	23	0.811
Started initially	7	4	9	
Added later	18	21	14	
Amphotericin B	11	7	14	0.460
Days on amphotericin-B, median (range)	9 (12–23)	9.5 (7–20)	8 (5–20)	0.95

[a]Between group 1 and group 3.
[b]Between group 2 and group 3.
[c]Between group 1 and group 2.

Table 3 Microbiologically documented Infections

Cultures	*AlloPBSCT*	*AutoPBSCT*	*CCT*
Urine			
E. coli	4	2	
Coagulase-negative staphylococci	3	3	1
Corynebacterium	1		
Staphylococcus aureus	1		
Blood			
Coagulase-negative staphylococci	5		
Staphylococcus aureus	1		1
K. pneumonia			1
Enterococcus			1
E. coli		3	
Staphylococcus epidermidis		1	
Alfa hemolytic streptococcus		1	
Candida	1		
Catheter			
Coagulase-negative staphylococci	8	2	1
Corynebacterium	1		
Staphylococcus epidermidis		1	
Acinetobacter spp.			

CCT groups, respectively. The duration of neutropenia was significantly shorter in the alloPBSCT group compared to the CCT group ($P < 0.001$) (Table 2). Febrile neutropenic days were 2 (0–9), 2 (0–12) and 3 (0–12) days in the alloPBSCT, autoPBSCT and CCT groups, respectively. There was no difference between the groups ($P < 0.05$).

Febrile episodes and infections

Eight-six percent of the patients in the alloPBSCT group (43/50), 93% of the patients in the autoPBSCT group (42/45), and 92% in the CCT group (46/50) had at least one febrile episode during their neutropenic period ($P > 0.05$). Microbiologically and/or clinically documented infection rates were 50% (25/50), 42% (19/45) and 48% (24/50) in these groups, respectively. Gram-positive pathogens, mostly coagulase-negative staphylococci, were the most frequent cause of bacteremias in all groups. The frequency of coagulase-negative staphylococcal infections was significantly higher in the alloPBSCT and the autoPBSCT groups compared to the CCT group ($P < 0.008$ and $P < 0.04$, respectively). In the CCT group, the rate of Gram-positive infections was similar to Gram-negative infections. As expected, catheter infections were frequent in the PBSCT group. In the alloPBSCT group, six patients had microbiologically defined catheter infections. In the autoPBSCT group, three patients had microbiologically defined catheter infections. There were 12 patients with pulmonary infections in the CCT group and two in the autoPBSCT group ($P < 0.05$).

Treatment

The median days with antibiotics were 8 (0–25), 9 (0–30) and 10.5 (0–28) in the alloPBSCT, autoPBSCT and CCT groups, respectively. The CCT group required antibiotics significantly longer compared to the alloPBSCT group ($P < 0.006$). A combination of beta-lactam antibiotic or a carbapenem + aminoglycoside was successful in controlling

fever in 17, 15 and 21 patients in the alloPBSCT, autoPBSCT and CCT groups, respectively ($P > 0.05$). Amphotericin-B was administered to 11, seven and 14 patients for a median of 9, 9.5 and 8 days in the alloPBSCT, autoPBSCT, and CCT groups, respectively ($P > 0.05$). Addition of a glycopeptide was made in 25 patients in the alloPBSCT group (seven in the initial regimen and 18 added later), in 25 patients in the autoPBSCT group (four in the initial regimen, 21 added later) and 23 patients in the CCT group (nine in the initial regimen, 14 added later). One septic shock was observed in the AutoPBSCT group. No death related to infection occurred in any group.

Discussion

There are some important points to be mentioned in this study. First of all, it is clear that Gram-positive microorganisms predominate in febrile neutropenia. This trend is demonstrated by the EORTC studies and was confirmed also by ourselves and other investigators.[4,5] This is the result of the increasing use of catheters,[6] and the use of ciprofloxacin as a prophylaxis is an added determinant. As can be seen in our study, the alloPBSCT group had a 40% and the autoPBSCT group had a 20% rate of Gram-positive infections, while the rate was only 8% in the CCT group. The prevalence of Gram-positive bacteremia was significantly higher in the PBSCT groups, compared to the CCT group ($P < 0.008$ and $P < 0.025$, respectively) (Table 2). While catheter usage is routine in the PBSCT group, this is not the case in the CCT group. Moreover, the CCT group did not receive any prophylaxis. Besides routine use of central venous catheters in PBSCT group, another factor that may effect the rate of Gram-positive infections is the high rate of mucositis in the PBSCT group, as demonstrated previously.

The CCT group had a high rate of pneumonia compared to the PBSCT groups ($P < 0.005$). Kolbe *et al*[7] observed a 5% rate of pneumonia in PBSCT patients and Maschmeyer *et al*[8] showed a rate of pneumonia of around 20% in patients receiving conventional chemotherapy. In our study, pneumonia occurred in 24% of patients in the CCT group. This fact can be explained by the long duration of neutropenia in the CCT group patients, which predisposes them to bacterial and fungal pneumonias. Other factors such as giving no prophylaxis (ciprofloxacin, TMP-SMX) and no growth factors can contribute to this high rate of pneumonia in the CCT group. Also, single room isolation and residence in the special care unit for the PBSCT patients may be factors in decreasing the rate of pneumonia, as there was no pneumonia in patients who received alloPBSCT in the neutropenic period.

Fungal agents were seen in one blood culture in the alloPBSCT group. This is not an unexpected finding, as the rate of fungal isolation is below 5% in most of the studies. Clinically suspected fungal infections were found in four patients, and they all occurred in the CCT group with pneumonia.

Although the duration of neutropenia, and the duration of antibiotic use was longer in the CCT group, their response to initial beta-lactam + aminoglycoside was better compared to the PBSCT groups. The factors, such as catheters, determining the outcome of infections other than neutropenia is more prominent in the PBSCT groups, and this results in the modification of the initial antibiotics. This is especially true for glycopeptides. Although neutropenia was of shorter duration in the alloPBSCT patients, the addition of amphotericin-B is nearly the same in all groups. This fact may be explained by the failure of the initial combination of antibiotics and the readiness of the physician to administer amphotericin-B to PBSCT patients compared to its use in CCT patients.

As a result, regardless of the care and treatment given to a patient with a hematological malignancy, nearly all patients (86–93%) experience febrile neutropenic episodes. Although the rate of infection is very high in this period, there is no mortality associated with it. The duration of neutropenia and the type of care given to a patient does not affect the rate of febrile episodes,[9] but does affect the type of infections, such as the higher rate of Gram-positive infections in PBSCT patients, and the high rate of pneumonias in CCT patients. The new policies in these high risk groups such as the use of prophylaxis in selected patients, an empirical approach to treatment in febrile neutropenic patients and changing strategies according to microbiological data are the main factors that contribute to our success in preventing infections during the initial neutropenic periods.

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