

DIABETES MELLITUS INCREASES THE RISK OF SERIOUS INFECTIONS FOLLOWING AUTOLOGOUS STEM CELL TRANSPLANTATION IN PATIENTS WITH MALIGNANT LYMPHOMA

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SUMMARY

Diabetes mellitus is a well known risk factor for infections, which remain a major cause of morbidity and mortality in patients treated with autologous peripheral blood stem cell transplantation (PBSCT). We evaluated infectious complications following transplantation in 132 consecutive patients with relapsed or refractory non-Hodgkin's lymphoma (n=101) and Hodgkin's disease (n=31) treated with PBSCT. Febrile neutropenia occurred in 86 (65.6%) patients at a mean of 6 days after transplantation (range 1-9, SD 1.59). Patients with diabetes mellitus had a clear predisposition for infectious complications following PBSCT. All 10 patients with diabetes developed febrile neutropenia. Compared to patients not having diabetes mellitus, they also had

significantly longer median time to defervescence (4 days vs. 2 days, Logrank P=0.03). Furthermore, diabetic patients had a higher incidence of serious infections: 60% of febrile episodes in these patients (vs. 30.3% in non-diabetics) were microbiologically proven bacteremias (P=0.07). Gram positive microorganisms were responsible for the majority of documented infections with Staphylococcus epidermidis as the most frequently isolated pathogen. Infections are serious but manageable complications of PBSCT, even in patients with unfavorable risk factors. Patients with lymphoma and diabetes mellitus undergoing stem cell transplantation are especially prone to infections during the neutropenic period following transplantation. Early empirical antimicrobial therapy tailored according to local microbiological epidemiology is essential for their optimal treatment.

INTRODUCTION

Diabetes is a common, increasingly frequent health condition associated with a wide range of metabolic, immune, and hormonal aberrations (1). Approximately

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250 million people worldwide are affected by diabetes mellitus and the number of adults with diabetes in the world is expected to rise to at least 300 million by 2025, making it a serious public health concern (2). Diabetics are more susceptible to infections, which have been clearly demonstrated in a number of studies (3-9). In these patients, suppression of cellular immunity seems to be one of the principal underlying mechanisms for the increased risk of infections (10,11). An increased risk of cancer, in particular pancreatic cancer, liver cancer, breast cancer, non-Hodgkin's lymphoma (NHL), and cancer of the endothelium among patients with diabetes has also been observed in several studies (1,12-15). Lymphomas are neoplastic transformations of normal lymphoid cells which reside predominantly in lymphoid tissues and are increasing in incidence for reasons which are unclear (16). They are subdivided into two major categories: NHL and Hodgkin's lymphoma.

Autologous stem cell transplantation is a standard therapeutic procedure for patients with primary refractory lymphomas and in patients with disease relapse. Autologous hematopoietic stem cells, collected nowadays more often from peripheral blood than from the patients' bone marrow, are reinfused after administration of an intensive myeloablative regimen. Patients treated with autologous hematopoietic cell transplantation (HCT) are at an increased risk of a variety of often serious and life-threatening infections based on the degree of immunosuppression and exposures (17). The major risk factors for infection during the first three weeks after HCT are mucositis and cutaneous damage, which disrupt the barriers of the skin and mucous membranes, neutropenia with resulting loss of phagocytic abilities, and organ dysfunction (18). Aerobic gram-positive and gram-negative bacteria account for most documented infections during this granulocytopenic period (19). Prior to the 1980s, gram-negative aerobes were the predominant organisms associated with nosocomial bloodstream infections. Since then, gram-positive aerobes (coagulase-negative staphylococci, *Staphylococcus (S.) aureus* and *Enterococcus*) and *Candida* spp. have

increased in relative importance (20-22). Risk factors for fungal infections, especially invasive candidiasis, include severe neutropenia, use of broad-spectrum antibiotics, organ dysfunction, mucocutaneous damage, and yeast colonization (23-27).

The aim of this study was to evaluate infectious complications in patients with lymphoma treated with peripheral blood stem cell transplantation (PBSCT) by determining the incidence, duration and etiology of febrile neutropenia. The additional goal was to investigate the impact of diabetes mellitus as a comorbid condition on these parameters.

PATIENTS AND METHODS

One hundred and thirty two consecutive patients (median age 44, range 19-71 years) with relapsed or refractory NHL (n=101) and Hodgkin's disease (n=31) treated with PBSCT at Department of Hematology, Merkur University Hospital from January 2000 to July 2009 were evaluated for infectious complications following autologous stem cell transplantation. Patient characteristics are summarized in Table 1. All but two patients received BEAM high-dose chemotherapy prior to PBSCT (carmustin 300 mg/m² on day -6, ara-c 2x200 mg/m² from day -5 to -2, etoposide 200 mg/m² from day -5 to -2, and melphalan 140 mg/m² on day -1). The remaining two patients received BEAC chemotherapy, a similar regimen with cyclophosphamide replacing melphalan. Routine peripheral blood cell counts were performed daily using an automated hematology analyzer (Sysmex XE-2100, Kobe, Japan). All patients received G-CSF 10 mcg/kg/day during neutropenia following transplantation. Ciprofloxacin 2x250 mg and fluconazole 200 mg were given orally as anti-infective prophylaxis. Body temperature was monitored every 2 h; in case of fever ≥ 38.5 °C or ≥ 38 °C on two consecutive measurements microbiological work-up was done. Biological samples were processed in the affiliated laboratory of Dr. Fran Mihaljević University Hospital for Infectious Diseases. Identification of isolates and susceptibility testing were done with routine methods. We considered bacteremias to be significant according to the Clinical Diagnostic Criteria (CDC): the isolation of a microorganism other

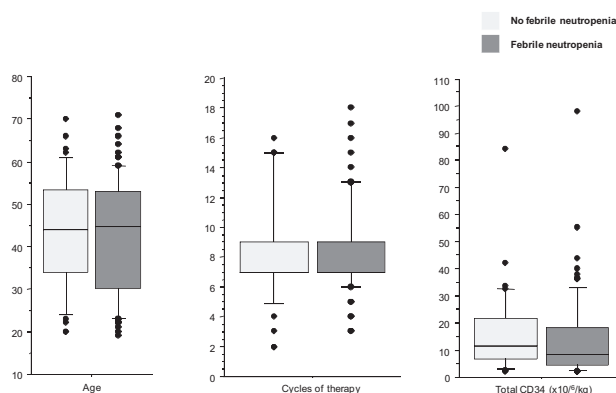
than skin contaminants in one blood culture with the presence of signs of infection, or the isolation of a microorganism in two consecutive cultures associated with signs of infection. Infections associated with positive cultures from other normally sterile sites (such as urine, cerebrospinal fluid, etc.) were classified as other microbiologically documented infections, while those with a clinical site involved (such as cellulitis, mucositis, pneumonia, etc.) were regarded as clinically documented infections. Empirical antimicrobial treatment with piperacillin and tazobactam was started in all patients not having a history of penicillin allergy. Further modifications of antimicrobial treatment were done according to IDSA guidelines (28). Prior to admission, all diabetic patients had been treated with insulin therapy or oral hypoglycemic agents. They all had diabetes mellitus before the treatment for lymphoma. When it was clinically indicated, during hospitalization for autologous stem cell transplantation they received short acting insulin (Actrapid HM, Novo Nordisk) in four daily doses, which is currently the basis of treatment in patients with diabetes mellitus with operative procedure or infections. The insulin dose was adjusted to blood glucose levels, which were measured at intervals of 4 to 8 hours (at 7.00 a.m., 11.00 a.m., 5.00 p.m. and 11.00 p.m.) with the use of capillary blood samples. Statistical analysis included descriptive statistics, with data expressed as mean \pm standard deviation, unless otherwise indicated. Chi square, t-test and the nonparametric Mann-Whitney test were used to assess statistical differences between two or more groups. Time to defervescence was analyzed with the Kaplan-Meier estimation method and the log-rank test. A *P* value less than 0.05 was considered statistically significant. All statistical analyses were performed with the StatView™ statistical program, version 5.0.1 (SAS Institute, Cary, NC, USA).

RESULTS

In this cohort of 132 patients, ten (7.5%) had diabetes mellitus diagnosed on the basis of World Health Organization criteria (29) as a comorbid condition. Diabetic patients were somewhat older than the rest of

patients (median age 53 vs. 44 years, t-test *P*=0.03). Compared with non-diabetic patients, they also received more cytotoxic chemotherapy, expressed as the number of lines and cycles of therapy for their lymphoma prior to PBSCT, but these differences were not statistically significant.

Figure 1. Incidence of febrile neutropenia in lymphoma patients following autologous stem cell transplantation according to age, cycles of previous therapy and CD34+ dose received.



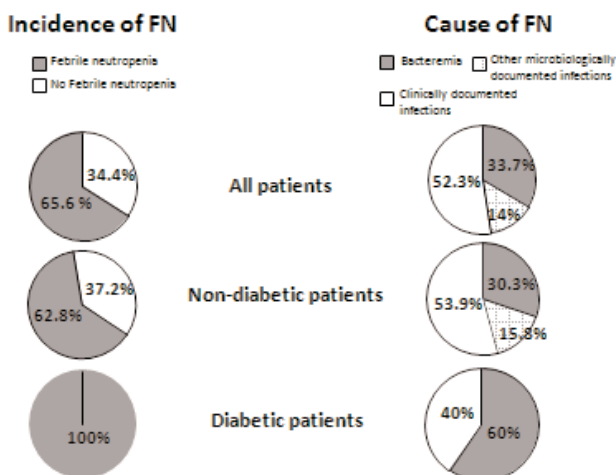
Febrile neutropenia occurred in 86 (65.6%) patients (Figure 1) at a mean of 6 days of transplantation (range 1-9, SD 1.59). Three patients, one of them with diabetes mellitus, died from sepsis (TRM=2.3%). Twenty nine (33.7%) patients had proven bacteremias, while 12 (14%) had other microbiologically documented infections (Figure 1), with oral mucositis and urinary tract infections being the most common clinical syndromes observed. Gram-positive microorganisms were the most common pathogens responsible for 62.1% of bacteremias, followed by gram-negative organisms in 34.5% and fungi in 3.4% of cases. *Staphylococcus epidermidis* and *Streptococcus* spp. were the most prevalent gram-positive pathogens responsible for 27.6% and 20.7% of bacteremias, respectively. *Escherichia coli* was the most common gram-negative pathogen, responsible for 17.2% of bloodstream infections, followed by *Pseudomonas aeruginosa* (6.9%).

A number of factors did not have any influence on the development of febrile neutropenia. The patients that developed fever and those free from it did not

Table 1. Patient characteristics

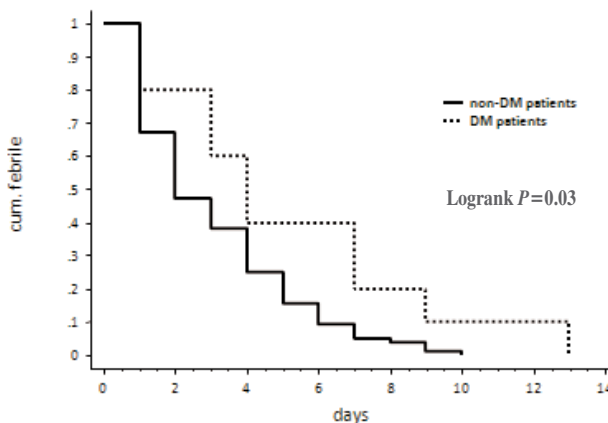
		No diabetes	Diabetes	
Total number		122	10	
Sex				<i>P</i> =NS
Male		61	7	
Female		61	3	
Diagnosis				<i>P</i> =NS
Non Hodgkin's lymphoma		94	7	
Hodgkin's disease		28	3	
Age (yrs)				<i>P</i> =0.03
	Median	44	53	
	Range	19-71	27-68	
Previous treatment				
Lines of chemotherapy	Median	2	2.5	<i>P</i> =NS
	Range	1-7	2-5	
Cycles of chemotherapy	Median	7	9.5	<i>P</i> =NS
	Range	2-16	3-18	
CD34 + cells (x10 ⁶ /kg) reinfused				<i>P</i> =NS
	Mean	14.8	11.3	
	Range	1.7-98.1	2.0-36.4	

Figure 2. Incidence and causes of febrile neutropenia (FN) in lymphoma patients following autologous stem cell transplantation.



differ according to age (*t*-test, *P*=0.80), number of previously received lines or cycles of therapy (Mann Whitney, *P*=0.35 and *P*=0.68, respectively) or dose of CD34+ cells (Mann Whitney, *P*=0.19). Results are shown in Figure 1. Cardiac (Chi square, *P*=0.86) or chronic obstructive pulmonary disease (Chi square, *P*=0.86) had no impact on the development of febrile neutropenia in patients post transplantation. Interestingly, patients with previous exposure to monoclonal antibodies or nucleoside analogs

Figure 3. Febrile neutropenic patients with lymphoma following autologous stem cell transplantation – time to defervescence depending on diabetes mellitus (DM) as comorbid condition.



developed febrile neutropenia less often than those that did not receive this kind of treatment (61.8% vs. 75.6% and 40% vs. 73%, respectively), but the differences did not reach statistical significance (Chi square, monoclonal antibodies *P*=0.13, nucleoside analogues *P*=0.11).

However, patients with diabetes mellitus had a clear predisposition for infectious complications following PBSCT (Figure 2). All ten patients with diabetes developed febrile neutropenia, while 37.2% of patients

not having diabetes remained without fever in the post-transplant period. Diabetic patients also had a higher incidence of serious infections: 60% of febrile episodes in these patients (*vs.* 30.3% in non-diabetics) were microbiologically proven bacteremias (Chi square, $P=0.07$). Compared to patients not having diabetes mellitus, they also had a significantly longer median time to defervescence (4 days *vs.* 2 days, logrank $P=0.03$, Figure 3). There was no significant difference according to the most common isolates between diabetic and non-diabetic patients with documented infections. Gram-positive isolates were detected in 50% of patients with diabetes and in 62.9% of patients without diabetes. Gram-negative microorganisms were isolated in 33% of febrile patients with diabetes and in 34.3% of patients free from diabetes. In 22.4% of non-diabetic patients, initial antimicrobial therapy was unsuccessful and needed to be modified. The same was necessary in 30% of diabetic patients.

DISCUSSION

Despite antimicrobial prophylaxis, the occurrence of febrile neutropenia was observed in about two thirds of all patients. Microbiological work-up did not always reveal the causative pathogen, as also reported from most other studies (18-27). Some have hypothesized that cell-wall deficient bacteria, usually gram-positive, might be responsible for these episodes with negative blood cultures following HCT (30). In this population of our patients, approximately half of febrile episodes were microbiologically documented infections, as also reported in the literature (31-34). These were mostly bacteremias, which remain life-threatening infections, especially in this population of heavily immunosuppressed patients. The pattern of causative organisms found in our study could be viewed as expected. Namely, after induction of selective intestinal decontamination against gram-negative microorganisms in the mid 1990s, gram-positive bacteria emerged as major pathogens causing bloodstream infections after hematopoietic stem cell transplantation. Our results are consistent with this general trend. The most prevalent gram-positive microorganism isolated in our population was

Staphylococcus epidermidis, a pathogen often causing catheter related bacteremia. The most likely explanations for the increased incidence of coagulase-negative staphylococcal infections are enhanced recognition and reporting of these organisms as valid bloodstream pathogens (as opposed to contaminants), the use of broad-spectrum antibiotics (selection pressure), and the increased use of intravascular devices. Coagulase-negative staphylococci and *S. aureus* commonly originate from the skin surface and track along the external surface of the catheter. In comparison, the hands of healthcare workers often introduce gram-negative organisms during manipulation of catheters or intravenous tubing.

The incidence of diabetes mellitus in patients included in our study was 7.5%, just slightly lower than in the general population in our country, where it is around 9% (2). All patients with lymphoma and diabetes mellitus developed febrile neutropenia following transplantation. Most of these episodes were microbiologically proven bloodstream infections. The susceptibility of diabetic patients to infections was demonstrated in a number of studies (3-9). A study from The Netherlands concluded that hyperglycemia was a significant factor leading to infections in hospitalized patients (3). Norwegian investigators demonstrated diabetes to be a significant risk factor for poor outcome of bacteremia in hospitalized patients (4). Both allograft rejection and risk of infections appeared to be higher in transplant recipients with diabetes. The increased risk of serious infections in diabetic heart transplant recipients in the early postoperative period was demonstrated in one study (5). In another, diabetic renal transplant recipients had a greater risk of acute allograft rejection and infection when perioperative glycemic control was poor (6). The increased risk of postoperative infections is also clearly associated with postoperative hyperglycemia among diabetics undergoing coronary artery bypass graft (7-9). Vascular insufficiency, sensory peripheral neuropathy and autonomic neuropathy as well as nephropathy are often associated with diabetes and represent host factors associated with an increased risk of infection. Patients with diabetes, particularly those injecting insulin daily, often have asymptomatic nasal

and skin colonization with *S. aureus*. Furthermore, according to an analysis of data from the National Health and Nutrition Examination Survey, diabetic patients that are colonized with *S. aureus* are more likely to have a methicillin-resistant *S. aureus* isolate than a susceptible one. Mucosal colonization with *Candida albicans* is also common. There are several organism-specific factors that predispose diabetics to infections, e.g., glucose-inducible proteins produced by *Candida albicans* which are homologous to complement receptor on phagocytes and ketone reductase produced by *Rhizopus* sp. (35,36).

The pathophysiology of inflammatory and anti-infective mechanisms in hyperglycemic conditions has been extensively investigated. It has been demonstrated that neutrophil chemotaxis and adherence to vascular endothelium, phagocytosis, intracellular bacterial activity, opsonization, and cell-mediated immunity are all depressed in diabetics with hyperglycemia (35,37,38). The release of tumor necrosis factor-alpha and interleukin-1 beta from lipopolysaccharide-stimulated macrophages is reduced in diabetic mice compared with control mice (39). The level of macrophage inflammatory protein 2, a mediator of lung neutrophil recruitment, is also significantly decreased in diabetic compared to control mice (40). The deficiency causes a delay in neutrophil recruitment in the lungs. Hyperglycemia impairs opsonophagocytosis by diverting NADPH from superoxide production into the aldose reductase-dependent polyol pathway (41). Insulin regulates the expression of several hepatic proteins that are involved in inflammatory response (42,43). In a rat model with induced inflammation, insulin treatment suppressed the level of proinflammatory cytokines, such as interleukin and TNF- α (44). In patients with diabetes or hyperglycemia, treatment with insulin led to a substantial decrease in the levels of inflammatory mediators (45,46). The state of hyperglycemia is also known to initiate a reactive oxygen species chain reaction and to activate several proinflammatory cytokines (47-49).

Our study demonstrated the patients with diabetes and malignant lymphoma treated with autologous stem cell transplantation to have an increased risk of infections. These results are in accordance with the findings of other studies mentioned above, which demonstrated that patients with diabetes had a higher incidence of infections, particularly severe infections. Therefore, the goal of achieving satisfactory regulation of glycemia has to be underlined, since it greatly influences the immune system and a number of inflammatory factors. Patients with diabetes mellitus and infection have increased insulin needs, and the needed amounts can indirectly reflect the success of treatment for infection. In a recent study in 537 diabetic patients with septic shock, there was no beneficial effect of intensive insulin treatment with mean glucose levels of 6.1 to 6.3 mmol/L because such a strict glucoregulation led to consequent frequent episodes of hypoglycemia, which were identified as an independent risk factor for death from any cause (50). The investigators assumed that unrecognized adverse effects of hypoglycemia on the brain or heart offset the potential beneficial effects of intensive insulin therapy. In our patients, glucoregulation was not so stringent and, as a consequence, no hypoglycemic episodes were observed in any of our patients. Short-acting insulin was administered in four daily doses and glucose values below 10 mmol/L were considered as satisfactory.

In conclusion, the results of our study demonstrated that diabetes mellitus increased the risk of serious infections in patients with malignant lymphoma treated with hematopoietic stem cell transplantation. However, the number of patients with diabetes mellitus in our study was too small for any definite conclusion. Diabetic patients should be monitored very closely for early signs of infections in the period following transplantation. Achieving a satisfactory regulation of glycemia and early empirical antimicrobial therapy, tailored according to local microbiological epidemiology, remain essential for the optimal treatment of infections in these patients.

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