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ORIGINAL ARTICLE

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Evaluation of potential risk factors for early infectious complications after autologous peripheral blood stem cell transplantation in patients with lymphoproliferative diseases

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Abstract A number of risk factors for the occurrence of neutropaenic fever after haematopoietic stem cell transplantation (HSCT) have been proposed. We were interested in whether these factors remain valid for several early infection-related outcomes when applied to a homogeneous group of patients in uni- and multivariate analyses. Therefore, we analysed 144 consecutive patients with lymphoproliferative disorders receiving autologous peripheral blood HSCT. Variables tested as potential risk factors for the occurrence of fever, documented infection (DI), microbiologically documented infection (MDI) or failure of first-line antimicrobial therapy were sex, conditioning regimen, prolonged neutropaenia, low number of CD34+ cells transplanted, purging, lack of selective gut decontamination, higher age and increased body mass index. In uni- and multivariate analyses, conditioning including total body irradiation was the only risk factor for the occurrence of fever, and neutropaenia ≥10 days was the only factor associated with failure of first-line antimicrobial therapy. None of the variables tested was associated with an increased risk for DI or MDI. This analysis suggests that a number of previously proposed risk factors actually are of minor clinical relevance for early infections in the majority of patients receiving autologous HSCT.

Keywords Autologous stem cell transplantation · High-dose chemotherapy · Infection · Risk factor

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Introduction

Infectious complications occur in most patients treated with high-dose chemotherapy (HDC) and haematopoietic stem cell transplantation (HSCT) and are still a major cause of treatment-related morbidity and even mortality [34]. Hence, the characterisation of risk factors for infectious complications is of great importance with respect to microbiological surveillance and monitoring as well as prophylactic and therapeutic antimicrobial strategies. Although a number of studies published over the past decade have already proposed several risk factors for infectious complications following HDC and autologous HSCT, it is difficult to draw final conclusions from these reports because of the lack of multivariate analysis in most studies and comparably small and/or heterogeneous patient populations [1, 4, 6, 10, 16, 23–25, 28–30]. Whilst some investigations also included allogeneic HSCTs, others did not consider differences between bone marrow and peripheral blood as stem cell source, or solid and haematopoietic tumours as underlying diseases. However, these factors have been suggested to affect several infection-related outcomes [1, 4, 10, 21, 29, 31]. In addition, most studies did not distinguish between early and late infectious complications, which have distinct characteristics. Whilst early infections, which are commonly defined as those occurring within 30 days after HSCT, affect most of all patients and mainly consist of fever of unknown origin (FUO) and bacteraemia, around 20% of patients develop late infections, for the most part varicella-zoster virus reactivation or pneumonia [7, 19, 25]. Furthermore, it has not been investigated whether the proposed risk factors are also valid for the development of documented in-

fections (DIs) or infections not responding to empirical first-line antimicrobial therapy, which can both be considered as complicated infections.

The purpose of this study was to determine whether previously proposed risk factors for transplant-related infections are actually valid for several early infection-related outcomes in the majority of patients undergoing HSCT. We therefore retrospectively analysed 144 consecutive patients with lymphoproliferative disorders treated with HDC and autologous peripheral blood HSCT at our institution over a 7-year period.

Patients and methods

Patients and conditioning regimens

Between December 1996 and October 2003, 144 consecutive patients with non-Hodgkin's lymphoma (NHL), Hodgkin's disease (HD) or multiple myeloma (MM) received HDC and autologous peripheral blood HSCT (Table 1). In patients who received tandem transplantations, only the first transplantation was considered. To be eligible for HDC, patients had to have a Karnofsky performance score of at least 80% and adequate end-organ function. All patients had either a short-term or long-term central venous catheter. All transplantations were analysed from the beginning of conditioning (day −8 to day −4 according to the regimen) until at least day +30 or discharge by a comprehensive review of the charts and microbiological test results. Conditioning regimens (Table 1) have been described in detail elsewhere [2]. In all patients, stem cell mobilisation was done using moderate dose chemotherapy regimens and granulocyte colony-stimulating factor (G-CSF) at least 2 months prior to ASCT.

Anti-infectious prophylaxis and treatment

Patients were treated with intensified hygiene measures in a tertiary care center on a separate transplantation ward in single rooms with high-efficiency particulate air filters and received a low-germ diet. G-CSF was given subcutaneously to all patients at a dose of 5 μg/kg body weight from day +7 until neutrophil recovery to >500/μl. Anti-infectious prophylaxis included trimethoprim-sulfamethoxazole (160 mg plus 800 mg twice daily from the beginning of conditioning until day −2, and on 2 days of the week after neutrophil recovery) and amphotericin B oral solution (200 mg five times daily from the beginning of conditioning until discharge) in all patients. Until July 2002 (100 patients), prophylaxis also consisted of acyclovir (400 mg every 8 h), fluconazole or itraconazole (200 mg daily) and selective gut decontamination with oral vancomycin (500 mg twice daily) plus oral paromomycin (500 mg every 8 h). These substances were generally given from the beginning of conditioning until neutrophil recovery.

According to recent guidelines, fever was defined as a single temperature >38.3 or ≥38°C over at least 1 h [3, 18]. Since all patients meeting these criteria received empirical antibiotic therapy, they were classified as having an infectious complication. Diagnostic procedures in all these patients included a thorough physical examination, multiple blood cultures and a chest radiograph, which were repeated in case of failure to respond to antimicrobial therapy. Additional investigations, such as a thoracic computed tomography (CT) scan, abdominal ultrasound or fiberoptic bronchoscopy, were done if considered necessary by the attending physician. Clinically documented infection (CDI) was defined as fever accompanied by adequate clinical findings such as pulmonary infiltrates or inflammation of the skin or soft tissue, and microbiologically documented infection (MDI) was defined as fever plus an appropriate microbiological test result [3]. For the diagnosis of bacteraemia, at least one positive blood culture was required. For coagulase-negative staphylococci (CNS) and corynebacteria, ≥2 separate blood cultures had to grow strains with identical antibiograms. All cases of fever other than CDI and MDI were classified as FUO. Neutropaenia was defined as the number of days from the 1st day with an absolute neutrophil count (ANC) <500/μl until the day before engraftment, for which 3 consecutive days with an ANC >500/μl were required.

Empirical first-line antibiotic therapy consisted of a third-generation cephalosporin plus an aminoglycoside in most cases. Some patients received monotherapy with a third-generation cephalosporin or a carbapenem. The majority of empirical second-line therapy regimens consisted of a carbapenem plus vancomycin. Patients with pulmonary infiltrates and those not responding to second-line antibiotics (if they received systemic antimycotic prophylaxis) or first-line antibiotics (if they did not receive systemic antimycotic prophylaxis) were treated with liposomal amphotericin B, voriconazole, itraconazole or caspofungin at standard doses. Response to antimicrobial therapy was defined as clinical resolution of symptoms and defervescence to lower than 37.5°C for more than 48 h.

Table 1 Underlying diseases and conditioning regimens. *BEAM* BCNU, etoposide, cytarabine, melphalan, *BCV* BCNU, cyclophosphamide, etoposide, *TBI* total body irradiation [2]

	Patients (*n*)
Diagnosis	
Non-Hodgkin's lymphoma	77
Hodgkin's disease	5
Multiple myeloma	62
Conditioning	
BEAM	36
BCV/augmented BCV	9
Melphalan	59
Melphalan+TBI	3
Cyclophosphamide+TBI	37

Statistical analysis

The association between patient and treatment characteristics and the occurrence of fever and documented infections and response to empirical first-line antimicrobial therapy was analysed by using binary logistic regression. The following variables were tested as potential risk factors: sex, conditioning regimen including TBI (vs chemotherapy only), duration of neutropaenia ≥10 days, transplantation of $<5\times10^6$/kg body weight CD34+ cells, purging (CD34-positive±CD20-negative selection), lack of selective gut decontamination, age and body mass index (BMI, in kg/m^2). Two separately analysed cut-off points were used for patient age (≥50 and ≥65 years) and BMI (≥25 and ≥30). First, univariate regression was done. If a variable showed significant association with an outcome, multivariate logistic regression using stepwise selection was done using SPSS 11.0. Results were considered statistically significant if p was <0.05.

Results

Distribution of risk factors

There were 81 male and 63 female patients. Median age was 54 years (range: 18–70), with 16 and 95 individuals aged ≥65 and ≥50 years, respectively. Median BMI was 24.9 (range: 17.3–44.6) with 22 obese (BMI ≥30), 49 overweight (BMI 25–29.9), 69 normal weight (BMI 18.5–24.9) and 4 underweight (BMI <18.5) patients, according to the current definition of the National Heart, Lung and Blood Institute http://www.nhlbi.nih.gov). Conditioning regimens included TBI in 40 patients (28%). The median number of CD34+ cells transplanted was 4.04×10^6/kg body weight (range: 1.88–19.8), and 97 patients (67%) were transplanted with $<5\times10^6$ CD34+ cells/kg body weight. Purging of the stem cell graft with CD34-positive±CD20-negative selection was done in 32 patients (22%). Median duration of neutropaenia was 8 days (range: 3–30), with 56 individuals (39%) being neutropaenic for ≥10 days.

Characteristics of early infectious complications

Of the 144 transplantations analysed, 125 (87%) were complicated by an early infection. Of these, 77 (62%) were classified as FUO, 44 as MDI (35%) and 8 (6%) as CDI. Three patients (2%) had a CDI (pulmonary infiltrate) plus an MDI (bacteraemia). The CDIs were seven pulmonary infiltrates and one folliculitis. The MDIs included 1 urinary tract infection (UTI) caused by *Escherichia coli*, 1 UTI (*E. coli*) plus *Streptococcus viridans* bacteraemia, 1 soft tissue infection caused by *Staphylococcus aureus*, and 41 bacteraemias, 5 of which were caused by more than one pathogen. Pathogens isolated from blood cultures were CNS (n=23), streptococci (n=12), enterococci (n=2), *S. aureus* (n=1), *Stenotrophomonas maltophilia* (n=1), *Pseudomonas aeruginosa* (n=2), *Pasteurella* species (n=1), *Corynebacterium* species (n=1) and *Morganella* species (n=1). There was no invasive fungal infection (IFI). Response to first-line empirical antibiotic therapy was observed in 65 patients (52% of patients with an infectious complication), and 60 patients (48%) required at least one change of the antimicrobial therapy.

Systemic antimycotic treatment because of pulmonary infiltrates or lack of response to antibiotic therapy was administered to 23 patients (18% of patients with fever and 16% of the whole study population). All patients were discharged afebrile except two who died of non-infectious complications during the observation period. One 61-year-old male patient with NHL died of intracranial haemorrhage on day +5 after BEAM conditioning and transplantation of 3.4×10^6 CD34+ cells/kg, and one 57-year-old man with MM who had received 2.1×10^6 CD34+ cells/kg after conditioning with melphalan succumbed to cardiac arrest on day +5.

Factors associated with the development and outcome of infectious complications

The only factor associated with an increased risk for the occurrence of fever in univariate analysis was TBI as part of the conditioning regimen (Table 2a). In multivariate analysis after a stepwise selection procedure, TBI remained a prognostic factor in the final model (Table 2b). The rather wide 95% confidence interval (CI) of 1.4–91.3 results from the fact that only 1 of 40 patients who received TBI as part of the conditioning did not develop fever and implies that the calculated risk ratio (RR) of 11.2 is less reliable. However, this does not impair the significance of TBI as a risk factor for the development of fever. None of the variables tested were associated with an increased risk for DIs or MDIs (data not shown) in univariate analysis. We did not test for potential risk factors for the development of CDIs because of their small number.

Table 2 Potential risk factors for the development of fever

Risk factor	Risk ratio	95% Confidence interval	p value*
a. Univariate analysis			
Gender (male)	1.3	0.5–3.8	0.5
TBI	8.1	1.1–63.3	0.045
Age ≥50 (65) years	1.9	0.7–5.1	0.2
	(1.1)	(0.2–5.1)	(0.9)
Neutropaenia ≥10 days	1.1	0.4–3.1	0.8
Purging	0.3	0.1–0.8	0.03
No gut decontamination	0.3	0.1–1.4	0.2
BMI ≥25 (30)	0.7	0.3–1.8	0.4
	(1.0)	(0.3–3.6)	(0.9)
$<5\times10^6$ CD34+ cells/kg body weight	0.8	0.3–2.1	0.6
b. Multivariate analysis			
TBI	11.2	1.4–91.3	0.023

*p values >0.1 are rounded

Table 3 Potential risk factors for failure of empirical first-line antibiotic therapy

Risk factor	Risk ratio	95% Confidence interval	*p* value*
a. Univariate analysis			
Gender (male)	1.1	0.5–2.0	0.8
TBI	0.9	0.4–1.8	0.7
Age ≥50 (65) years	1.1	0.6–2.2	0.7
	(0.8)	(0.3–2.3)	(0.8)
Neutropaenia ≥10 days	1.1	1.0–1.3	0.043
Purging	0.5	0.2–1.1	0.07
No gut decontamination	0.8	0.4–1.6	0.5
BMI ≥25 (30)	1.3	0.7–2.4	0.5
	(1.2)	(0.5–3.1)	(0.7)
$<5\times10^6$ CD34+ cells/kg body weight	1.0	0.5–2.1	0.9
b. Multivariate analysis			
Neutropaenia ≥10 days	1.1	1.0–1.3	0.041

*p values >0.1 are rounded

All patients except the two individuals who died of non-infectious complications eventually responded to antimicrobial therapy, and there were no invasive fungal infections. As a parameter of unfavourable outcome, we therefore chose failure of first-line antimicrobial therapy. Duration of neutropaenia ≥10 days significantly increased the risk of requiring at least one change in antibiotic therapy in univariate analysis (Table 3a), which was confirmed in multivariate analysis (RR: 1.1, 95% CI: 1.0–1.3; Table 3b). None of the other variables tested showed an association with failure of first-line antimicrobial therapy (Table 3a).

Discussion

The incidence and type of early infectious complications we observed correspond well to previous reports. There were only a few pulmonary infiltrates, and no patient developed an IFI although 44 of 144 (31%) did not receive systemic antimycotic prophylaxis. It may be argued that some IFIs have gone undiagnosed since we initiated empirical antimycotic therapy in a timely manner and did not routinely use thoracic CT scans or new serologic diagnostic procedures. However, this seems unlikely since IFIs in neutropaenic patients with haematopoietic malignancies are characterised by a low response rate and high mortality. Hence, our observations support the notion that IFIs are rare after autologous HSCT, regardless of whether prophylaxis is given or not.

In contrast to previous reports including different proportions of patients receiving TBI [19, 25, 28], we found TBI to be associated with an increased risk for the occurrence of fever in the early post-transplant period. Although it is conceivable that TBI results in a higher rate of infections particularly by damaging the gastrointestinal mucosal barrier, TBI might also cause fever in the absence of infection by increased cytokine release [17, 32]. This may be supported by the fact that we did not observe an association of TBI with DIs or MDIs, that the rate of bacteraemias caused by typical gastrointestinal commensals was low and that TBI was not associated with an increased risk of failure of first-line antibiotic therapy.

Neutropaenia lasting 10 days or more was the only factor associated with a slightly increased risk of failure to respond to first-line antimicrobial therapy. This is in accordance with previous findings [25] and suggestions that the application of haematopoietic growth factors to shorten the period of neutropaenia may reduce the occurrence of complicated infections following autologous HSCT [9, 12].

Purging of the stem cell graft was not associated with an increased risk for infectious complications in our study and even seemed to reduce the risk of fever in univariate analysis. This is in contrast to two previous reports on an increased rate of complicated infections including infection-related deaths following autologous HSCT with CD34-positive±CD20-negative selection [1, 15]. However, these studies included comparably small numbers of patients and multivariate analysis was not performed, whereas another study done in a larger group of patients with MM found that CD34+ selection was associated with a slightly impaired recovery of dendritic cells, but not with an increased rate of infections [8]. Although it appears from the latter study and our observations that purging itself is not a risk factor for the development of fever or complicated infections, it is still possible that it contributes to a more pronounced immunosuppression and thereby severe infection in individual patients, which should be kept in mind.

It has been suggested that the use of at least 5×10^6 CD34+ cells/kg body weight significantly shortens duration of neutropaenia [20] and reduces the incidence of fever and duration of antibiotic therapy following autologous HSCT [28]. In our study, autografting with less than 5×10^6 CD34+ cells/kg body weight was not a risk factor for the occurrence of fever, DIs or MDIs, or for failure of first-line antimicrobial therapy. The only study reporting on a decrease in infectious complications by using $>5\times10^6$ CD34+ cells/kg body weight was done in a very heterogeneous group of patients with both haematopoietic and solid malignancies who were treated with 13 different conditioning regimens [28]. Thus, we believe that a CD34+ cell dose of less than 5×10^6/kg body weight should no longer be considered a relevant risk factor for early infectious complications following autologous HSCT for haematopoietic malignancies. This is supported by an investigation which found that only the transplantation of very low numbers of CD34+ cells ($<0.75\times10^6$/kg body weight) increases fever episodes and antibiotic requirement late after autologous HSCT [26].

In patients undergoing allogeneic and autologous HSCT, both overweight and underweight have been related to an increased non-relapse mortality [11, 13, 14]. In addition, two studies in patients receiving autologous HSCT for haematopoietic malignancies not only reported on an increased mortality in overweight patients, but also found an association between body weight and infectious complications [23, 30]. Interestingly, whilst one study described an increased rate of DIs [23], the other observed a decrease in the

incidence and duration of fever in overweight patients [30]. This inconsistency is most likely caused by the small number of overweight individuals included in these studies and the lack of multivariate analysis. Hence, although an abnormal BMI seems to be associated with increased mortality following HSCT, it should not be considered to be a risk factor for early infectious complications.

Patients at higher age are frequently excluded from HDC protocols because of an anticipated poor tolerance. Our observations demonstrate that older patients are at least not at increased risk for febrile episodes or complicated infections early after autologous HSCT, thereby supporting a recent report on similar rates of engraftment and transplant-related mortality in patients aged at least 60 years compared to younger patients [33].

Selective gut decontamination, which has been discussed controversially [5], is associated with considerable costs and may potentially cause resistance. Since omitting selective gut decontamination was not a risk factor for the occurrence of fever or complicated infections in our analysis, it appears it may be safely left out in the setting of autologous HSCT.

The parameters we included in this analysis represent the majority of risk factors suggested by published reports or expert opinion. However, because of the retrospective nature of this single-centre investigation, we were not able to include factors such as physician-, centre- or nursing-related variables. Another frequently addressed factor is disease status, which we did not include in this analysis because we did not find a higher rate of infectious complications in patients with stable or progressive disease compared to patients in complete or partial remission in a previous study [2].

This investigation demonstrates that in patients with lymphoproliferative disorders undergoing HDC and peripheral blood autologous HSCT, TBI and prolonged neutropaenia are associated with an increased rate of febrile episodes and failure of first-line empirical antimicrobial therapy, respectively. However, a number of previously proposed risk factors for the development of infectious complications appear to be of minor clinical relevance for the majority of patients undergoing HSCT in the early post-transplant period.

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