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Research Article

Aminoglycoside-free interventional antibiotic management in patients undergoing haemopoietic stem cell transplantation

Aminoglycosid-freies interventionelles Antibiotikamanagement bei Patienten mit hämopoetischer Stammzelltransplantation

Abstract

The position of aminoglycosides within interventional antibiosis in the early phase after stem cell transplantation has not been fully clarified so far although their use can induce serious renal impairment. To investigate this question early-infection data from 152 patients undergoing 195 allogeneic and autologous stem cell transplantations were investigated. Prophylaxis and treatment of infections followed international standards; however, aminoglycosides were omitted to avoid additional risks such as ototoxicity and nephrotoxicity and increased selection of resistant pathogens. Costs were another aspect.

The overall-incidence of infections was 78% (152/195) and 67 patients showed more than one episode of infection. Fever of unknown origin and bacteriaemia/septicaemia dominated the spectrum of infections. The overall-response to interventional regimen consisting of β-lactam or carbapenem plus glycopeptides was 48%. Aminoglycosides were given in three patients in the late course of disease. Overall mortality was 15/195 (7.7%) and clearly related to infection in nine cases mostly due to mould infection. A comparison with previous published literature showed no hint for inferiority of 'aminoglycoside-free' antibiotic management in stem cell transplant patients. In conclusion, the present analysis supports the policy to omit aminoglycosides in the therapy of early infections in patients undergoing stem cell transplantation to avoid additional toxicity.

Keywords: high-dose therapy, stem cell transplantation, conditioning therapy, neutropenia, infection

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Zusammenfassung

Die Bedeutung der Aminoglycoside für das empirische antibiotische Management in der Frühphase nach Stammzelltransplantation ist mit Ausnahme des Risikos schwerer Nierenschäden nicht vollständig geklärt. Zur Klärung dieser Frage wurden die Daten der Frühinfektion von 152 Patienten mit 195 allogener und autologer Stammzelltransplantation analysiert. Die Prophylaxe und Therapie der Infektionen erfolgte gemäß internationalen Standards mit der einzigen Ausnahme, dass auf den Einsatz von Aminoglycosiden verzichtet wurde, um ototoxische und nephrotoxische Risiken zu vermeiden und dem Selektionsdruck mit Verbreitung resistenter Erreger zu begegnen. Die Einsparung von Kosten war ein zusätzlicher Aspekt.

Die Inzidenz der Frühinfektion betrug 78% (152/195). 67 Patienten waren von mehr als einer Infektionsepisode betroffen, wobei Fieber unklarer Genese und Bakteriämie/Septikämie dominierten. Auf das interventionelle Regime mit β-Lactam oder Carbapenem + Glyopeptide reagierten 48% der Patientrn. Aminoglycoside wurden nur bei drei Patienten in der Spätphase der Erkrankung verabfolgt. Die Mortalität betrug

15/195 (7,7%) und war in neun Fällen eindeutig mit der Infektion, meist verursacht durch Schimmelpilze, assoziiert. Der Vergleich mit der Literatur ergibt keinen Anhalt für eine Unterlegenheit des Aminoglycosid-freien Antibiotika-Managements für Patienten mit Stammzelltransplantation. Damit stützt die vorliegende Studie die Möglichkeit des Verzichts auf Aminoglycoside in der Therapie der Frühinfektion von Patienten mit Stammzelltransplantation zur Vermeidung toxischer Risiken.

Introduction

Infections contribute significantly to morbidity and mortality after stem cell transplantation [1], [2], [3]. The diagnosis of neutropenic fever demands immediate onset of broad-spectrum antibiosis and rapid escalation in the case of non-response [4], [5]. Addition of a systemic antimycotic compound effective against *Candida spp.* and moulds is recommended within 48 to 96 hours after initiation of first line antibiotic administration, if fever has not resolved. Aminoglycosides have been a standard drug for therapy of neutropenic fever for several years because of suggested additional clinical activity i.e. synergistic effects in combination with β-lactam antibiotics; however, considerable adverse effects are nephrotoxicity and ototoxicity [6], [7].

Allogeneic and autologous stem cell transplantation have emerged during the last two decades and can currently applied to patients older than seventy and to heavily pretreated patients with partly impaired organ functions [8], [9], [10]. Additionally, nephrotoxic cytostatics such as cisplatinum are essential components of some high-dose protocols to gain optimal anti-tumour effects against male germ cell cancer [11]. Especially in multiple myeloma, renal function may be impaired due to underlying disease. In the allogeneic setting an immunosuppressive therapy with cyclosporine-A or tacrolimus is mandatory to prevent graft rejection and graft-versus-host disease [8], [9]. Administration of drugs such as foscarnet, trimethoprim-sulfmethoxazole or acyclovir for anti-infectious prophylaxis or therapy after transplantation can be associated with considerable nephrotoxicity or it may require a normal renal function [12].

The position of aminoglycosides in first line antibiotic therapy of high-risk patients with neutropenic fever has been discussed controversial. Some trials show equality of monotherapy with broad spectrum β-lactam compared to aminoglycoside-containing combination therapy [13], [14], [15]. Other investigators used quinolones as combination partner for β-lactams instead of aminoglycosides [16], however, this policy is limited in stem cell transplantation since most patients here receive quinolones for antibacterial prophylaxis [12]. Marie et al. described in their meta-analysis significant advantages when aminoglycosides are used [17]: The rate of defeverescence was higher, the duration of fever shorter, less vancomycin was needed, and the overall success-rate was higher. As a consequence, most guidelines recommend both, single β-lactam therapy or combination with aminoglycoside for interventional antibiosis in neutropenic patients [4], [5].

To address the important issue of nephroprotection by avoidance of aminoglycosides in stem cell transplantation, an aminoglycoside-free interventional antibiotic management for therapy of neutropenic fever or early infections of patients undergoing haemopoietic cell transplantation has been conducted at Greifswald University Hospital since 1996. Results of this study are presented and discussed here.

Patients and methods

Patients, diagnoses and transplantations

The present investigation followed a retrospective longitudinal surveillance protocol. Surveillance data were created in routine cooperation with an extern professional infection control practitioner from the Institute of Hygiene and Environmental Medicine.

Between 1996 and 2004 a total of 152 patients underwent 195 transplant procedures after written informed consent. In 48 cases (24.6%) the recipient received an allograft from a matched related donor (n=21; 10.8%) or from an unrelated donor (n=27; 13.8%). In the latter situation, maximal one HLA-antigen mismatch was accepted. In 147 cases (75.4%) the transplantation was carried out with G-CSF-mobilised autologous stem cells. 43 transplantations were second or third transplantations. Thirty subsequent autologous transplantations were performed as part of a therapy protocol, mainly for male germ cell cancer or for multiple myeloma. Thirteen subsequent allogeneic transplantations were carried out for salvage therapy of relapsed disease. Each transplantation was considered as a separate patient in this analysis for statistical reasons. 121 (62.1%) patients were male and 74 (37.9%) were female. The median patient age was 50.7 years (median; range: 17.3–70.7) years.

Indications for stem cell transplantation were acute and chronic leukaemias (n=40; 20.5%), malignant lymphomas (n=55; 28.2%), multiple myeloma (n=35; 17.9%), myelodysplastic syndrome (n=6; 3.1%), and solid tumours (n=59; 30.3%). Details are shown in Table 1. Stem cell transplantation was performed in 124 cases (63.6%) in the early course of disease (first complete or partial remission, first chronic phase of CML, or transplantation as a part of the primary treatment). The remaining 71 transplantations (31.4%) were done in more advanced disease.

Table 1: Diagnoses

Diagnosis	n	%
Acute leukaemia	21	10.8
Chronic leukaemia	19	9.7
Germ cell cancer	24	12.3
Hodgkin's lymphoma	7	3.6
Multiple Myeloma	35	17.9
Myelodysplastic syndrome	6	3.1
non-Hodgkin's lymphoma	48	24.6
Other solid tumours	27	13.8
Sarcoma	8	4.1

Conditioning regimen was busulphan-based in 81 cases (41.5%). 25 patients (12.8%) received treosulphan/fludarabine prior to allogeneic transplantation. VIC was given as high-dose therapy prior to autologous stem cell reinfusion in 35 cases (18.0%) and high-dose melphalan was given for multiple myeloma in 31 cases (15.9%). Total body irradiation in conjunction with chemotherapy was used in 6 cases (3.1%) and one patient (0.5%) received an allogeneic stem cell boost without prior conditioning. Haemopoiesis was stimulated with G-CSF after transplantation until engraftment.

Prophylaxis of GvHD in the allogeneic setting was with cyclosporine-A and short course methotrexate or mycophenolate-mofetil, depending on the conditioning therapy. 29/48 patients (60.4%) undergoing allogeneic transplantation were treated with antithymocyte globulin. Metronidazole was given for anaerobic gut decontamination in the allogeneic setting.

Antimicrobial prophylaxis

Allogeneic transplantations were done in rooms conditioned with HEPA-filtrated air (H 13 point use of filters) in our transplant unit. Autologous transplantations were also conducted in these rooms. Only when no HEPA-conditioned room was available, patients in the autologous setting were nursed in single-rooms on the normal ward. Antimicrobial prophylaxis was initiated lately with begin of conditioning therapy [12]. In most cases (n=171; 87.7%) a third-generation quinolone was given, in four cases combined with a β-lactam active against gram-positive bacteria. Eight transplantations (4.1%) in the autologous setting were conducted without antibacterial prophylaxis. The remaining 17 patients received miscellaneous antibiotics, mainly β-lactams, for prophylaxis.

Fluconazole was given for systemic antimycotic prophylaxis in 127 cases (65.1%) and 64 patients (32.8%) received itraconazole. In six of these cases the initial drug was switched during further course to itraconazole (n=2), fluconazole (n=2), or conventional amphotericin-B (0.2 mg/kg/d). One patient each received voriconazole, caspofungin or conventional amphotericin-B (0.2 mg/kg/d), or was transplanted without antimycotic prophylaxis. Amphotericin-B suspension was given orally at least four times daily upon tolerability. Reasons for discontinuation were emesis or mucositis.

Pneumocystis jirovecii prophylaxis was done with monthly pentamidine-inhalations after an initial loading dose (n=87; 44.6%) or with trimethoprim-sulfmethoxazole three times per week (n=18; 9.2%). The remaining 90 patients (46.2%) were managed without Pneumocystis-prophylaxis. *Pneumocystis-jirovecii*-prophylaxis was mandatory in all patients undergoing allogeneic transplantation and depended upon the therapy-protocol in the autologous setting.

A total of 80 patients received either acyclovir (n=79; 40.5%) or foscarnet (n=1; 0.5%) for antiviral prophylaxis. It was mandatory in allogeneic transplantation. Patients undergoing autologous stem cell transplantation received prophylactic virustatics only as a secondary prophylaxis, upon regulations of a therapy protocol or if the underlying disease was Hodgkin's lymphoma.

Antibacterial prophylaxis was stopped after the onset of antibiotic therapy and antimycotic prophylaxis after the onset of systemic antifungal therapy for suspected or documented infection.

Diagnosis of infection

Diagnosis of fever of unknown origin (FUO) was made after the occurrence of a body temperature of ≥38.2 °C. Resolution of fever was defined as the first of three days with a maximum temperature of 37.5 °C. Site specific infections were diagnosed according to the results of clinical examinations or the results obtained by specific diagnostic procedures.

Antimicrobial therapy

Broad spectrum antibiotic therapy was started immediately when the temperature rose above 38.2 °C or higher, or for documented or suspected bacterial infection (e.g.: positive x-ray examination, clinical and local signs of infection). Additionally, a significant increase of CRP to at least ca. 60 mg/l in the early or middle phase of expected neutropenia was – in conjunction with clinical performance – an indication for antimicrobial escalation. Blood cultures were drawn prior to antibiotic therapy and then daily until the fever resolved. X-ray examination of the chest was carried out. Urine culture, oral, rectal and nose swabs were taken prior to antibiotics and serologic tests for Aspergillus or Candida antigen were performed when a mycotic infection was suspected. Special diagnostic procedures such as computed tomography x-ray, bronchioalveolar lavage or obtaining tissue biopsies were carried out when necessary.

First line antibacterial therapy consisted of a β-lactam with activity against *Pseudomonas spp.* Generally, ceftazidime was the first drug given, only in cases where cisplatinum was part of high-dose regimen the antimicrobial therapy was begun with imipenem/cilistatin. In cases with increased risk factors for Gram-positive infections vancomycin or teicoplanin was added initially. Factors to

be considered with increased risk for Gram-positive infection were a severe mucositis, a suspected CVL-associated sepsis, known colonisation with MRSA or Streptococcus pneumoniae or a critical ill patient [4], [18]. Antimicrobial therapy was modified or escalated when fever did not respond within 24 to 48 hours. The kind of modification depended upon the clinical course and the results of microbial and other laboratory investigations. First modification was supplementation with a glycopeptid, when not part of initial therapy. Next steps were either the change of the initially given β-lactam or the addition of a macrolid-antibiotic or the escalation of antifungal therapy. Since less toxic antimycotics became available during the time of observation, there was a trend to escalate earlier with newer substances such as liposomal amphotericin-B, modern azoles or echinocandines than with conventional amphotericin-B. Clinical signs suggestive of mycosis included fever or pulmonary infiltrates that did not respond to antibiotics or a suspicious CT-scan of the lung.
Further modifications of antimicrobial therapy such as fosfomycin or clindamycin for treatment of soft tissue infections were made according to the results of surveillance cultures and serological tests, and from the clinical features and course of infection.
Antiviral therapy with ganciclovir or foscavir was initiated after diagnosis of viral infection by culture or molecular methods, or in the case of clinical evidence of viral infection. In case of a suspected Herpes simplex or Varicella zoster virus reactivation, acyclovir was either initiated, dose-increased or replaced by another virustatic.
Antibacterial and antimycotic therapy was discontinued when the patient had recovered with his neutrophile granulocytes (>1/nl) and signs of infection and fever have completely resolved.

Data collection and analysis

Data were collected with database software Access (Microsoft, Munich, Germany) and analysed using the computer software Excel (Microsoft, Munich) and GraphPad Prism for Windows (GraphPad Software, San Diego, California, USA). The independent T-test or the Mann-Whitney U-test was used for the comparison of two groups, and datasets with more than two subgroups were compared by variate analysis (LSD/Bonferroni).

Results

Engraftment, neutropenia and graft-versus-host disease (GvHD)

Patients undergoing autologous transplantation were slightly older than those undergoing allogeneic transplantation (median 52.5 years; range: 17–71 vs. median 47.5 years; range: 18.5–65; $p<0.05$, Mann-Whitney U-test). 187 patients engrafted with 0.5 leukocytes/nl between day 0 (cells never below 0.5L/nl) and day +25 (median day +9) after transplantation. 1.0 leukocytes/nl were reached by 185 patients also on day +9 (median; range: 0–27 days). Engraftment of leukocytes was significantly faster after autologous stem cell transplantation than after allografting: **0.5L/nl:** 8 days (median; range: 0–12 days) *vs.* 12 (median; range: 0–25 days) ($p<10^{-9}$, Mann-Whitney U-test); **1.0L/nl:** 9 days (median; range: 7–14) *vs.* 13 (median; range: 0–27 days) ($p<10^{-10}$, Mann-Whitney U-test). 16/48 (25%) patients after allogeneic stem cell transplantation suffered from moderate to severe acute graft-versus-host disease (stage 2: n=6; stage 3: n=9; stage 4: n=1).

Fever and infections

Preliminary it must be remarked, that not all patients with an infection developed fever and that from some patients with positive microbial results more than one pathogen was isolated. As the consequence, the congruency of results needs not necessarily to be 100%.
124 patients developed at least one episode of fever during stem cell transplantation without differences between allogeneic and autologous patients. Median onset of fever was day +6 (range: –1–47). Fever occurred significantly early in the autologous setting (median on day +5.5, range: –1–14) compared to day +7.5 (median, range: –1–47) in the allogeneic setting. Fever resolved after three days (median; range: 1–29) without differences between both modalities.
A second episode of fever occurred more frequently after allogeneic transplantation (12/48) than after autologous transplantation (16/147), $p<0.02$, chi-square. As a consequence, the cumulative duration of fever was significantly longer after allogeneic transplantation than after autologous transplantation (median 6 days; range: 1–56 vs. 3 days, range: 1–24; $p<0.001$; Mann-Whitney U-test).
A total of 152 (77.9%) patients developed at least one episode of infection under stem cell transplantation. An overview of observed infections gives Table 2. Most frequent primary manifestation of infection was fever of unknown origin (FUO) with 74 cases (37.9%) followed by microbiologically confirmed bacteriaemia with or without signs of sepsis (n=26; 13.3%). Seventeen (8.7%) infections were related to the central venous line. Urinary tract was focus of primary infection in 9 cases (4.6%) followed by pneumonitis and enteritis (8 cases each, 4.1%). Other diagnoses like infection of the central nervous system or soft tissue not related to the CVL were rare.
The analysis of subsequent (non-first) infections gave a less clear graduation: Most frequent was enteritis (n=17; 11.2%) followed by bacteriaemia with or without signs of sepsis (n=17; 11.2%). 43 patients (22.1%) passed procedure of stem cell transplantation without any signs of infection.

Microbial pathogens

Isolated microbial pathogens are shown in Table 3. The microbes were only considered after isolation from non-natural sites. In total, 63 pathogens were isolated from

Table 2: Primary and subsequent infections. Percentages in last column are related to n=152 patients with *any first infection* listed in the second column.

	first infection		subsequent infection		cumulative infections	
Infection	**n**	**%**	**n**	**%**	**n**	**%**
FUO	74	37.9	5	3.3	79	36.1
bacteriaemia/septicaemia	26	13.3	15	9.9	41	18.7
pneumonitis	8	4.1	7	4.6	15	6.8
central venous line	17	8.7	0	0.0	17	7.8
enteritis	8	4.1	17	11.2	25	11.4
soft tissiue	3	1.5	0	0.0	3	1.4
miscellaneous	2	1.0	15	9.9	17	7.8
urinary tract	9	4.6	6	3.9	15	6.8
viraemia	3	1.5	2	1.3	5	2.3
CNS	2	1.0	0	0.0	2	0.9
all infections	*152*	*77.9*	*67*	*44.1*	219	100.0
patients without infections	*43*	*22.1*	*85*	*55.9*	n.a.	n.a.
number of patients analysed	*195*	*100.0*	*152*	*100.0*	n.a.	n.a.

Table 3: Isolated microbial pathogens

	first infection		subsequent infection		cumulative results	
Pathogen	**n**	**%**	**n**	**%**	**n**	**%**
Aspergillus spp.	3	4.8	2	4.7	5	4.7
C. difficile	6	9.5	7	16.3	13	12.3
Candida albicans	0	0.0	2	4.7	2	1.9
Candida non-albicans	1	1.6	1	2.3	2	1.9
Chlamydia spp.	1	1.6	1	2.3	2	1.9
Coagulase-negative Staphylococci	16	25.4	7	16.3	23	21.7
Corynebacteriae	1	1.6	1	2.3	2	1.9
Enterobacteriacaeae	9	14.3	5	11.6	14	13.2
Enterococcus spp.	7	11.1	2	4.7	9	8.5
Fusarium spp.	1	1.6	0	0.0	1	0.9
Non-fermenting	3	4.8	4	9.3	7	6.6
Miscellaneous	2	3.2	2	4.7	4	3.8
Pseudomonas spp.	2	3.2	2	4.7	4	3.8
Staphylococcus aureus	1	1.6	1	2.3	2	1.9
Streptococcus spp.	3	4.8	0	0.0	3	2.8
Toxoplasma	1	1.6	0	0.0	1	0.9
Viruses	6	9.5	6	14.0	12	11.3
Total number of microbial pathogens	*63*	*100.0*	*43*	*100.0*	106	100.0

the first episodes of infection and 43 from subsequent episodes. The predominant bacteria in the first episode were coagulase-negative staphylococci (CoNS) (n=16; 25.9%), followed by enterobacteriacaeae (n=9; 14.3%) and enterococci (n=7; 1.1%). *C. difficile* was identified in 6 cases (9.5% of isolates). *Aspergillus spp.* was isolated in three cases (4.8%), one isolate of *Fusarium solanii* and one isolate of Candida non-albicans (1.6%, each) were found. *Pseudomonas spp.* and other non-fermentative Gram-negative rods represent 2 (3.2%) and 3 (4.8%) of isolated pathogens from first infections, respectively. Further details are given in Table 3.

Between the first to subsequent infection a decrease of the number of pathogens and different changes of the prevalence of the species could be observed. The most important change can be referred to CoNS – with 10% decrease. In this context it must be necessarily pointed out, that in cases with identification of *Pseudomonas spp.* as the pathogenic agent, the clinical signs of infection have resolved prior to availability of microbiological results. The proportion of virus isolates increased from 10 to 14%. Please refer to Table 3 for further details.

Response to therapy

Since an initiated interventional antibiosis was discontinued after engraftment and resolution of infection and in not all cases with more than one episode of infection

the points of end and onset of both episodes could not be clearly discriminated, only the definite resolution of infection was analysed.

A total of 155 patients received antimicrobial therapy for documented or suspected infection (Table 4). 74 patients (47.7%) responded to therapy with ceftazidime or imipenem/cilistatin or meropenem in combination – either initially or sequentially – with a glycopeptid (vancomycin or teicoplanin). In 34 cases (21.9%) the resolution of infection could be clearly related to engraftment of leukocytes. Antimycotic therapy was successful in 6 patients (3.9%). In 11 cases (7.1%) no response to antimicrobial therapy was seen and the response could neither be correlated to a distinct drug nor to engraftment in 10 cases (6.5%).

Table 4: Response to antimicrobial therapy. N=40 patients without antimicrobial were not included in this analysis.

	Patients	
Substance	**n**	**%**
β-lactam or monobactam plus glycopeptid	74	47.7
macrolid	5	3.2
quinolone	2	1.3
clindamycin	2	1.3
antimycotics	6	3.9
miscellaneous	3	1.9
ganciclovir	4	2.6
metronidazole	2	1.3
tetracyclin	2	1.3
cumulative response to therapy	***100***	***64.5***
engraftment	34	21.9
unclear	10	6.5
no reponse	11	7.1
total	*155*	*100.0*

Another view was to correlate the response of infection to the step of antimicrobial escalation: 76 patients (49%) responded to steps one and two of antibacterial escalation and n=10 (6.5%) to the third step followed by antimycosis (n=6; 3.9%). Only 3 patients (1.6%) responded after a further (4th) antibacterial line.

Outcome

137 patients undergoing 180 transplantations (92.3%, related to transplantations) were discharged or transferred to another ward and 15 patients (7.7%) have died at median on day +20 (range: 3–130 days) after stem cell transplantation (Table 5). The interval showed highly significant differences between patients undergoing allogeneic transplantation compared to patients after autologous transplantation. Discharge, transfer or death was at median on day +17 (range: 6–116) after autologous and on day +38 (range: 3–130) after allogeneic transplantation ($p<10^{-10}$, Mann-Whitney U-test).

Three patients died after autologous and 12 after allogeneic transplantation. The majority of these patients were heavily pre-treated and 10/15 patients were transplanted in higher (>2nd) remission or with active disease. Additionally, for six of these patients it was a second transplantation. The death could be clearly related to an infection in 9/15 cases (60%).

Aspergillus spp. was culturally identified as the pathogen in 4/9 (44.4%) infection-related deaths and in one other case clinical course and CT-scan of the lung made the diagnosis of an invasive mycosis probable. Five other patients have died from sepsis; however, here the microbial pathogens remained unknown. The remaining five patients have died from acute GvHD (n=1), relapse of malignancy alone (n=2) or relapse with pulmonary bleeding (n=1) and from a cerebral (n=1) bleeding. All together, 7 of these 15 patients (46.7%) had severe complications which could not be correlated to infection (Table 5).

Discussion

The present retrospective analysis investigates the efficacy of an 'aminoglycoside-free' interventional antibiotic regimen for the therapy of infections in the acute phase of patients undergoing allogeneic or autologous haemopoietic cell transplantation. Aminoglycosides were not excluded by a study-protocol; however, it was policy to avoid them whenever possible because of their considerable side effects. Varying Medline-searches revealed surprisingly, that the newest publications investigating early infections in stem cell transplantation patients in general have been published approximately 10 years ago.

Overall, 77.9% (n=152) of the patients developed signs of infection. Neutropenic fever and bacteriaemia or septicaemia represented 54.8% of infections and 22.1% of all patients remained free of signs of infection. The duration of a first episode of fever was at median 3 days and the median cumulative duration of fever was 3 days after autologous and 6 days after allogeneic transplantation. These results are not different to those from preceding publications, where the use of aminoglycosides was usual. Krüger et al. reported similar results in 1999 [3]: about 60% of infections in their investigation were FUO and septicaemia. Cumulative duration of fever was in the present investigation slightly shorter than in the cited (Table 6). Comparison of the present results with preceding studies is hampered by at least two facts: In the nineties was the use of marrow harvests common and nowadays the use of growth-factor mobilised stem cells is the standard. One result of this shift is a shorter duration of neutropenia: The engraftment was reported in 1999 at median on day +17 compared to day +9 in the present investigation [3]. Second, the percentage of allografts and autografts varies between publications [2], [3], [19]. However, since it has been accepted that infections in the pre-engraftment phase are comparable in

Table 5: Deaths during early phase of transplantation

Pat.-#	Age	G	Diagnosis Type of TX	Engraft-ment	Complications	Reason for death	Site of infection	Microbial pathogen	Death related to infection
1	39	M	NHL allo-mud	yes	Pulmonary aspergillosis	Infection	Lung	Asp. fumigatus	yes day +51
2	42	F	NHL allo-mrd	not evaluable	Sepsis pulmonal aspergillosis	Infection	Lung	Asp. fumigatus	yes day +3
3	53	M	CLL allo-mud	no	Acute GvHD IV°	GvHD, MOF	Urinary tract, resolved	E. coli	no day +50
4	53	F	ALL allo-mrd	yes	Septic shock disseminated mycosis	MOF mycosis	Lung, generalised (DX by CT-scan)	not specified	yes day +21
5	56	M	ALL allo-mrd	no	Leukaemic relapse aspergillosis	Relapse	Lung	Asp. spp.	secondary day +130
6	33	M	NHL allo-mrd	yes	Relapse	MOF	FUO, resolved	n.a.	no Day +30
7	61	M	NHL Auto	yes	Sepsis	MOF	FUO, Sepsis	unknown	yes day +15
8	57	F	MM Auto	yes	Sepsis	MOF	FUO, Sepsis	unknown	yes day +26
9	57	M	NHL allo-mrd	yes	Relapse Pulmonary bleeding	Pulmonary bleeding	n.a.	n.a.	no day +18
10	64	F	CML allo-mud	yes	GvHD III°, Sepsis	MOF	Sepsis	unknown	yes day +35
11	59	F	AML allo-mud	no	Sepsis, graft failure, aspergillosis	MOF, aspergillosis	#1: Sepsis, (resolved) #2: Aspergillosis	#1: St. maltophilia #2: Asp. spp.	yes day +35
12	55	M	AML allo-mud	no	Graft failure, sepsis	MOF, sepsis, graft failure	Sepsis	E. faecium	secondary day +27
13	37	M	GCC auto	no	CNS-toxicity III°	Sepsis, MOF	Sepsis	unknown	yes day +6
14	51	M	MDS Allo-mrd	no	Graft failure	MOF, cerebral bleeding	Sepsis, pneumonitis	unknown	secondary day +37
15	59	F	AML Allo-mud	no	Pulmonary bleeding	Pulmonary bleeding	FUO (resolved) Lung (Aspergillosis)	Asp. Fumigatus	Yes day +18

Table 6: Studies investigating early infections in transplant patients

Author	Aminoglycosides within interventional antibiosis?	Time to defeverscence, Median days (range) (1st episode)	Response to antimicrobial therapy	Gram-negative rods (%)	Patients (% allogeneic TX)
Kolbe et al. [2]	yes	4 (1–18)	69.4%	6.9%	66 patients, no allo-TX
Krüger et al. [3]	yes	5 (0–85)	66.9%	21.4%	409 patients allo-TX: n=245 (59.9%)
Offidani et al. [19]	yes	3 (1–29)	data not provided	36.2%	150 patients, no allo-TX
Presented investigation	no	3 (1–29)	64.5%	23.6%	195 patients, allo-TX: n=48 (24.6%)

both settings two additional publications were available for comparison [2], [19].

The present investigation gives no hint for emerging of Gram-negative bacteria when aminoglycosides are avoided. More than 25% of all isolated pathogens were Gram-positive cocci. Enterobacteriacaeae, *Pseudomonas spp*. and other non-fermentative rods represent here 23.6% of isolated pathogens comparing to 21.4% in a previous publication [3]. In contrast Offidani et al, who have used aminoglycosides in first line antibiosis, reported 36.2% Gram-negative rods between isolated pathogens [19].

The overall response rate to first and second line interventional antibiosis was approximately 50% and only slightly increased by supplementation with antimycotics. This observation could be a result of improved antimycotic prophylaxis. Only 65% of the patients in the present investigation received fluconazole alone and all other patients received a substance active against *Aspergillus spp*. and Candida non-albicans. In contrast, flucanozole-prophylaxis was standard in the early nineties. The cumulative response rate to antimicrobial therapy was 64.5% and again comparable to the results published by the other groups (Table 6) [2], [3], [19].

Three patients have died after autologous stem cell transplantation from multi-organ failure and sepsis without isolation of any pathogen. Krüger et al. reported in 1999 also three early deaths after autologous transplantation (3/157; 1.9%) [3]. Kolbe et al. [2] and Offidani et al. [19] reported no deaths, however an early mortality of 2% (3/148 patients) is within international standard. Furthermore, one of these patients suffered additionally from chemotherapy-related CNS-toxicity. Mortality after allogeneic transplantation could only be compared to the results from Krüger from 1999, since the other publications were restricted to the autologous setting. The actual mortality rate was 25% compared to 15.1% in 1999 [3]. However, here it is necessary to mention the high risk profile of the patients which underwent allogeneic transplantation and have died during procedure (Table 5). Furthermore, the rate of unrelated donors in the allogeneic setting was actually 56.3% compared to 22.5% in the preceding presentation. Even this analysis gave no hint for an increased contribution of Enterobacteriacaeae or non-fermentative Gram-negative rods to mortality.

In conclusion, the presented data support the concept of an 'aminoglycoside-free' interventional antibiotic management despite the fact, that quinolones are not available as a reasonable combination partner for empiric therapy since their use is common in prophylaxis [12]. In comparison to other investigators no increase of infections, of Gram-negative pathogens or hints for an inferior outcome were observed. The investigation of a potential benefit of aminoglycosides in the setting of stem cell transplantation within a prospectively randomised trial would normally be the next step, however, conducting such a trial would aggravated by the fact that transplant patients are very heterogeneously. As the consequence, the presented results encourage the use of an 'aminoglycoside-free' antibiotic management since considerable side effects can be avoided [16], [20].

Notes

Authorship

T.K. and G.D. contributed equally to the paper and share the secondary authorship.

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References

1. Leather HL, Wingard JR. Infections following hematopoietic stem cell transplantation. Infect Dis Clin North Am. 2001;15(2):483-520.

2. Kolbe K, Domkin D, Derigs HG, Bhakdi S, Huber C, Aulitzky WE. Infectious complications during neutropenia subsequent to peripheral blood stem cell transplantation. Bone Marrow Transplant. 1997;19(2):143-7.

3. Kruger W, Russmann B, Kroger N, Salomon C, Ekopf N, Elsner HA, et al. Early infections in patients undergoing bone marrow or blood stem cell transplantation – a 7 year single centre investigation of 409 cases. Bone Marrow Transplant. 1999;23(6):589-97.

4. Link H, Bohme A, Cornely OA, Hoffken K, Kellner O, Kern WV, et al. Antimicrobial therapy of unexplained fever in neutropenic patients - guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO), Study Group Interventional Therapy of Unexplained Fever, Arbeitsgemeinschaft Supportivmassnahmen in der Onkologie (ASO) of the Deutsche Krebsgesellschaft (DKG-German Cancer Society). Ann Hematol. 2003;82 Suppl 2:S105-17.

5. Zinner SH. Relevant aspects in the Infectious Diseases Society of America (IDSA) guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever. Int J Hematol. 1998;68 Suppl 1:S31-4.

6. Mingeot-Leclercq MP, Glupczynski Y, Tulkens PM. Aminoglycosides: activity and resistance. Antimicrob Agents Chemother. 1999;43(4):727-37.

7. Nakashima T, Teranishi M, Hibi T, Kobayashi M, Umemura M. Vestibular and cochlear toxicity of aminoglycosides – a review. Acta Otolaryngol. 2000;120(8):904-11. DOI: 10.1080/00016480050218627

8. Baron F, Storb R. Allogeneic hematopoietic cell transplantation as treatment for hematological malignancies: a review. Springer Semin Immunopathol. 2004;26(1-2):71-94. DOI: 10.1007/s00281-004-0165-3

9. Niederwieser D, Maris M, Shizuru JA, Petersdorf E, Hegenbart U, Sandmaier BM, et al. Low-dose total body irradiation (TBI) and fludarabine followed by hematopoietic cell transplantation (HCT) from HLA-matched or mismatched unrelated donors and postgrafting immunosuppression with cyclosporine and mycophenolate mofetil (MMF) can induce durable complete chimerism and sustained remissions in patients with hematological diseases. Blood. 2003;101(4):1620-9. DOI: 10.1182/blood-2002-05-1340

10. Maris MB, Sandmaier BM, Storer BE, Chauncey T, Stuart MJ, Maziarz RT, et al. Allogeneic hematopoietic cell transplantation after fludarabine and 2 Gy total body irradiation for relapsed and refractory mantle cell lymphoma. Blood. 2004;104(12):3535-42. DOI: 10.1182/blood-2004-06-2275

11. Bokemeyer C, Schmoll HJ. Treatment of advanced germ cell tumours by dose intensified chemotherapy with haematopoietic growth factors or peripheral blood stem cells (PBSC). Eur Urol. 1993;23(1):223-9.

12. Kruger WH, Bohlius J, Cornely OA, Einsele H, Hebart H, Massenkeil G, et al. Antimicrobial prophylaxis in allogeneic bone marrow transplantation. Guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Haematology and Oncology. Ann Oncol. 2005;16(8):1381-90. DOI: 10.1093/annonc/mdi238

13. Del FA, Menichetti F, Martino P, Bucaneve G, Micozzi A, Gentile G, et al. A multicenter, double-blind, placebo-controlled trial comparing piperacillin-tazobactam with and without amikacin as empiric therapy for febrile neutropenia. Clin Infect Dis. 2001;33(8):1295-301.

14. Hess U, Bohme C, Rey K, Senn HJ. Monotherapy with piperacillin/tazobactam versus combination therapy with ceftazidime plus amikacin as an empiric therapy for fever in neutropenic cancer patients. Support Care Cancer. 1998;6(4):402-9. DOI: 10.1007/s005200050184

15. de Pauw BE, Deresinski SC, Feld R, Lane-Allman EF, Donnelly JP; The Intercontinental Antimicrobial Study Group. Ceftazidime compared with piperacillin and tobramycin for the empiric treatment of fever in neutropenic patients with cancer. A multicenter randomized trial. Ann Intern Med. 1994;120(10):834-44.

16. Peacock JE, Herrington DA, Wade JC, Lazarus HM, Reed MD, Sinclair JW, et al. Ciprofloxacin plus piperacillin compared with tobramycin plus piperacillin as empirical therapy in febrile neutropenic patients. A randomized, double-blind trial. Ann Intern Med. 2002;137(2):77-87.

17. Marie JP, Vekhoff A, Pico JL, Guy H, Andremont A, Richet H. Neutropenic infections: a review of the French Febrile Aplasia Study Group trials in 608 febrile neutropenic patients. J Antimicrob Chemother. 1998;41 Suppl D:57-64.

18. Einsele H, Bertz H, Beyer J, Kiehl MG, Runde V, Kolb HJ, et al. Infectious complications after allogeneic stem cell transplantation: epidemiology and interventional therapy strategies. Guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). Ann Hematol. 2003;82(Suppl 2):S175-S185.

19. Offidani M, Corvatta L, Olivieri A, Rupoli S, Frayfer J, Mele A, et al. Infectious complications after autologous peripheral blood progenitor cell transplantation followed by G-CSF. Bone Marrow Transplant. 1999;24(10):1079-87. DOI: 10.1038/sj.bmt.1702033

20. Bliziotis IA, Michalopoulos A, Kasiakou SK, Samonis G, Christodoulou C, Chrysanthopoulou S, et al. Ciprofloxacin vs an aminoglycoside in combination with a beta-lactam for the treatment of febrile neutropenia: a meta-analysis of randomized controlled trials. Mayo Clin Proc. 2005;80(9):1146-56. DOI: 10.4065/80.9.1146

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