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Antimycotic Therapy with Liposomal Amphotericin-B for Patients Undergoing Bone Marrow or Peripheral Blood Stem Cell Transplantation

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Suspected deep or systemic mycosis in patients undergoing high-dose therapy and autologous or allogeneic bone marrow transplantation (BMT) requires an immediate systemic antimycotic therapy. Intravenous therapy with the standard drug conventional amphotericin-B is associated with severe adverse effects like nephrotoxicity and chills. Furthermore, BMT patients often receive other potential nephrotoxic drugs such as CsA or virustatics. In this study, we report 74 BMT-patients treated with liposomal amphotericin-B for culture-documented aspergillosis (n = 5) or candidiasis (n = 6), or for serologically (n = 35) or clinically suspected mycosis or as prophylaxis (n = 2). Therapy was initiated with a median dose of 2,8 (0,64–5,09) mg/kg body-weight and continued for 13 (1–55) days. The drug was excellently tolerated and only in one was therapy stopped due to severe chills and fever. Severe organ impairment was not observed under therapy with liposomal amphotericin-B. Creatinine decreased in five patients after an increase under preceding therapy with the conventional formulation. Influence of liposomal amphotericin-B on bilirubin and transaminases was difficult to evaluate due to therapy-related toxicity, veno-occlusive disease (VOD), and graft-versus-host disease (GvHD). 10/11 culture-positive patients died from aspergillosis (5/5) or candidiasis (5/6), but in 9/11 of these subjects the immunity was additionally compromised by GvHD, steroid therapy, and VOD. Liposomal amphotericin-B was effective in preventing relapse of systemic mycosis in 10/12 patients with a history of aspergillosis (n = 11) or candidiasis (n = 1). We conclude, that favourable toxicity of liposomal amphotericin-B should encourage dose escalation studies of liposomal amphotericin-B randomised against the conventional formulation and that the comparison of patients undergoing BMT with patients under standard chemotherapy might be difficult because of additional risk factors of the BMT-patients.

Keywords: Bone marrow transplantation, neutropenia, liposomal amphotericin-B, invasive mycosis, fungal sepsis

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1. INTRODUCTION

Invasive or systemic fungal infections are a major cause of death in patients with haematologic malignancies undergoing antineoplastic treatment with therapy-related neutropenia.[1] The risk of patients undergoing allogeneic related or matched unrelated bone marrow transplantation for systemic mycoses additionally is increased by therapeutic or graft-versus-host disease induced immunosuppression.[2] Even suspected fungal infection in immunocompromised patients requires an immediate broad spectrum antimycotic therapy.[3,4] Several antimycotic agents have been introduced into therapy during the last years, however, the gold standard for the treatment of deep or systemic mycotic infections in neutropenic or immunosuppressed patients still remains the intravenous infusion of amphotericin-B, an agent damaging the cell walls of susceptible fungi.[5]

The intravenous administration of amphotericin-B is associated with a high rate of adverse effects like fever, chills, emesis, and renal injury ranging from a mild increase of serum creatinine to severe organ failure necessitating haemodialysis.[6,7] A culturally documented diagnosis of systemic candidiasis or aspergillosis in aplastic patients is difficult to obtain and indicates, in our experience, advanced disease. Invasive procedures such as open lung biopsy in cases of suspected aspergillosis endanger the patients by bleeding complications and secondary infections.[8] Thus, the decision to initiate treatment with the relatively toxic drug amphotericin-B mainly relies on clinical experience. To overcome the toxic side effects of amphotericin-B, the drug has been combined with lipids by several investigators, with different approaches ranging from a simple dilution in lipid emulsions commonly used for parental nutrition to a liposomal encapsulation of amphotericin-B.[9,10] The liposomal encapsulation of the drug enlarged the therapeutic index significantly allowing a dose increase from usually 1 mg/kg bodyweight up to 6mg/kg with minimal adverse effects, even in patients receiving several other nephrotoxic agents like cyclosporine-A, aminoglycosides, or virustatics.[11]

Several investigators reported favourable results after treatment with liposomal amphotericin-B even after failure of the conventional drug, and an increased effectiveness of liposomal amphotericin-B compared to the conventional formulation was described.[12] Currently, the use of the liposomal formulation is mainly based on favourable toxicological data, in-vitro studies examining the susceptibility of clinical fungus isolates to both, conventional and liposomal amphotericin-B, have been neglected. Only a few investigators have performed susceptibility testings with different results.[13,14] There is evidence, that the in-vitro antifungal activity of amphotericin-B-lipid combinations depends on the quality and structure of the lipids employed. Animal studies have mainly examined pharmacokinetic parameters and only Karyotakis *et al.* have compared outcome of neutropenic mice experimentally infected with Candida strains after treatment with conventional and liposomal amphotericin-B.[15]

Patients treated with myeloablative high-dose therapy often develop severe organ toxicity and receive several drugs potentially associated with toxicities and adverse effects.[16] Thus, a low rate of side effects for a drug which is administered often based only on clinical suspicion, is important in these special patients. In this report, we describe our single centre experience with liposomal amphotericin-B in 74 patients undergoing myeloablative high-dose therapy and allogeneic or autologous bone marrow or peripheral blood stem cell transplantation.

2. MATERIAL AND METHODS

Over the five year period from March 1991 to April 1996, 74 patients undergoing myeloablative high-dose therapy and allogeneic bone marrow transplantation or autologous stem cell rescue were treated with liposomal amphotericin-B for documented or suspected invasive or systemic mycoses. 41 patients were male, the median age was 32 years (range from 8 months to 64 years). The underlying disease was acute leukaemia in 40 cases, chronic leukaemia in 8 and non-Hodgkin's lymphoma and severe aplastic anaemia in 7 and 6 cases respectively. Other diagnoses are listed in table I. 40 patients received an HLA-identical related allograft, 5

TABLE I Patient Characteristics (n=74)

Diagnosis	Patients	(%)	Tx-type	Patients	(%)
AML	24	(32,4)	allo-mrd	40	(54,1)
ALL	16	(21,6)	allo-mm	5	(6,8)
CML	8	(10,8)	allo-hid	1	(1,4)
NHL	7	(9,5)	mud-id	9	(12,2)
SAA	6	(8,1)	mud-mm	1	(1,4)
MM	4	(5,4)	allo-PBSC	2	(2,7)
M. Farquahr	3	(4,1)	syngeneic.	2	(2,7)
MDS	1	(1,4)	auto-PBSC	5	(6,8)
MPS	1	(1,4)	auto	5	(6,8)
MLD	1	(1,4)	auto-purged	4	(5,4)
Neurobl.	1	(1,4)			
Sarcoma	1	(1,4)			
Thalas.	1	(1,4)			

Legend to table 1: **AML**: acute myeloic leukaemia, **ALL**: acute lymphoblastic leukaemia, **CML**: chronic myeloic leukaemia, **NHL**: non-Hodgkin's lymphoma, **MM**:multiple myeloma, **SAA** severe aplastic anaemia, **MDS**: myelodysplastic syndrome, **MLD**: metachromatic leukodystrophia, **MPS**: myeloproliferative syndrome, **Neurobl.**: neuroblastoma, **Thalas.**: Thalassaemia, **Tx-type**: type of transplantation, **allo-mrd**: allogeneic HLA-matched-related donor, **allo-mm**: 1 HLA-mismatched related donor, **allo-hid**: allogeneic haploidentical related donor, **mud-id**: HLA-matched-unrelated donor, **mud-mm**: 1 HLA-mismatched related donor, **allo-PBSC**: allogeneic peripheral blood stem cells, **auto-PBSC**: autologous peripheral blood stem cells, **auto**: autologous marrow, **auto-purged**: autologous purged marrow

sex: male: 41 (55%) female: 33 (45%)

age: median: 30 years, range: 8 months–64 years

an allograft carrying a mismatch and one was grafted from a HLA-haploidentical sibling. Two patients were transplanted with both marrow and G-CsF mobilised stem cells from a HLA identical relative. 10 patients were transplanted with a graft from a matched unrelated donor including one patient carrying one mismatch. Two further patients were transplanted from a syngeneic donor. An autograft was reinfused in 14 patients consisting of G-CsF mobilised peripheral blood stem cells (n = 5), or autologous bone marrow (n = 9) including four mafosfamide-purged harvests (table 1). 12 (16,2%) patients had a history of suspected or documented Aspergillus- or Candida-pneumonia.

Lately antimicrobial prophylaxis was initiated lately one day prior to high-dose therapy containing systemic quinolone-antibiotics in 72 cases. Two children received cotrimoxazole/colistin. All patients were nursed in isolation rooms with positive pressure filtered air, 39 patients were treated under laminar air flow conditions additionally. 58 patients received flucanozole, 10 patients itraconazole and two patients both for antimycotic prophylaxis. Additionally, 13 of these patients received amphotericin-B nebulised and nine patients orally. Two subjects with a short time interval after a previously documented Aspergillus pneumonia received liposomal Amphotericin as antimycotic prophylaxis. Two patients received oral amphotericin-B alone and one patient together with intravenous infusion of conventional amphotericin-B.

Broad spectrum antibiotic therapy was started immediately, when the temperature rose above 38,2°C or higher. Blood cultures were drawn prior to antibiotic therapy and then daily until fever decreased. An x-ray examination of the chest was done. Serologic tests for Aspergillus or Candida antigen were done at least weekly. Urine culture, oral, rectal and nose swabs were done prior to antibiosis and than at least once weekly. Systemic antifungal treatment was initiated when fever did not respond to antibiotics within 72 hours, when patients developed a second episode of fever after successful antibiotic therapy or for documented or suspected mycosis. Suspicious clinical

signs for mycosis were at least fever or pulmonary infiltrates not responding to antibiotics.

3. RESULTS

Fungal Infections

74 patients undergoing high-dose therapy and allogeneic or autologous bone marrow or blood stem cell transplantation were treated between March 1991 until March 1996 with liposomal amphotericin-B for documented or suspected mycosis. The indication for the treatment with liposomal amphotericin-B was at least fever without response to broad spectrum antibiotic therapy. One patient had isolated computed-tomography-documented aspergillosis of the CNS. 27 patients had pulmonary signs on chest x-ray examination, two of these combined with culture-documented Aspergillus-sinusitis. 45 patients had serologic evidence for invasive candidiasis (n = 37), aspergillosis (n = 3), or both (n = 5). Fungi were cultured from specimens of eleven patients. Candida krusei was cultured from blood, stool, urine and bronchoalveolar lavage of three patients, and together with Candida glabrata from BAL of a fourth patient. Two patients developed sinusitis and pneumonia caused by Aspergillus fumigatus and flavus, respectively. In three patients, Aspergillus fumigatus pneumonia was diagnosed by BAL. Candida lambica and Candida glabrata sepsis occurred in one patient each. Details of culture positive patients are given in table V.

Treatment with Liposomal Amphotericin-B

Liposomal amphotericin-B was given for primary antimycotic therapy in 29 patients including two patients receiving the drug for antimycotic prophylaxis after an Aspergillus pneumonia under preceding antineoplastic therapy. In 44 cases, the antimycotic therapy was switched to the liposomal formulation after a preceding course of conventional amphotericin-B given for a median of 4 (1–52) days. The reasons for the switch were an increased serum creatinine above 1,4mg/dl (n = 20), intolerable side effects (n = 9), no response (n = 9), or increasing serum creatinine which was initially below 1,5mg/dl under therapy with conventional amphotericin-B. Patients were treated with liposomal amphotericin-B for a median of 13 days (1–55), starting with a dose of 2,8 (0,64–5,09) mg/kg bodyweight. At the end of the course, the dose was increased to 2,93 (1–5,13) mg/kg bodyweight (table II). In one case, the drug was withdrawn because of intolerable side effects after one day of treatment.

Side Effects of Treatment with Liposomal Amphotericin-B

Clinical side effects occurred in 3/74 patients (4,05%) requiring the withdrawal of the drug in one case due to massive chills and fever. Two patients developed headache, abdominal pain, and fever allowing the continuation of therapy under concomitant medication. The course of laboratory parameters creatinine, bilirubin, OT and PT is shown in table IIIa and IIIb. The creatinine decreased under therapy with liposomal amphotericin-B in 5/20 and remained constant in 2/20 patients with an increase above 1,4 mg/dl under preceding conventional amphotericin-B. Potassium losses are a well-known side effect under therapy with conventional amphotericin-B. Due to severe, i. v. morphine-requiring mucositis, nearly all patients undergoing high-dose therapy require total parenteral nutrition. Thus, the only parameter we evaluated, is the time of additional intravenous potassium substitution during the course of liposomal Amphotericin-B. In 27/74 (36,5%) patients, additional potassium substitution was not necessary. 47/74 (63,5%) patients required additional potassium infusions. Overall, in the 74 patients on 22% (0–100%) of the days of treatment with liposomal amphotericin-B additional potassium

TABLE II Treatment with Liposomal Amphotericin-B

Parameter	Unit	Median	Range
start dose	mg/kg bodyweight	2,8	0,64–5,09
end dose	mg/kg bodyweight	2,93	1–5,13
overall dose	mg/kg bodyweight	36,02	2,79–186,89
overall dose	mg (absolute)	2400	60–11610
duration	days	13	1–55

TABLE IIIA Maximum values for laboratory parameters under therapy with liposomal amphotericin-B compared to the base level prior to the onset of the drug. Given is the number of patients and the percentage in brackets.

Increase up to % of u. n.v.	Creatinine	Bilirubin	OT	PT
decrease	11 (14,9)	11 (14,9)	4 (5,4)	10 (13,5)
no change	11 (14,9)	6 (8,1)	4 (5,4)	5 (6,8)
≤150%	35 (47,3)	13 (17,6)	11 (14,9)	16 (21,6)
≤200%	9 (12,2)	10 (13,5)	10 (13,5)	11 (14,9)
≤400%	7 (9,5)	14 (18,9)	21 (28,4)	18 (24,3)
≤500%	1 (1,4)	4 (5,4)	5 (6,8)	4 (5,4)
>500%	0	16 (21,6)	19 (25,7)	10 (13,5)

u. n. v.: upper norm value

infusions were necessary. Sodium losses known from conventional Amphotericin-B could not be evaluated. An increase of bilirubin above the base level was associated with GvHD of stage 3 or more, with veno-occlusive disease of the liver (VOD), or both. 37/57 (65%) of patients with raising bilirubin had GvHD ≥ 3 or/and VOD compared to 13/30 (43%) patients without. It should be pointed out, that all patients received concomitant nephrotoxic and hepatotoxic drugs such as cyclosporine, methotrexate, antibiotics and virustatics. Thus, it is difficult to evaluate the nephrotoxicity and hepatotoxicity of liposomal amphotericin-B in our collective. However, in 5 patients creatinine decreased after the onset of liposomal amphotericin-B.

Efficacy of Treatment with Liposomal Amphotericin-B

Eleven patients developed a culture positive invasive or systemic mycosis after transplantation. Aspergillus spp. were isolated in 5 and Candida spp. in 6 cases. Corresponding fungal antigen was detected serologically in 10/11 patients. All but one patient with Candida lambica sepsis died in multi-organ failure from mycosis. This man was cured by liposomal amphotericin-B and discharged on day +36 after allogeneic bone marrow transplantation. All patients with culture proven mycosis were at a very high risk for mycotic infections due to primary or secondary aplasia after transplantation or due to graft-versus-host disease requiring intensive steroid therapy. The course of fungal antigens and details of culture-positive patients are given in tables IV and V. A woman with an increasing titre for Aspergillus antigen from 1/8 to 1/16 under therapy died from an highly suspected and ct-documented cerebral aspergillosis. An autopsy was not permitted.

Twelve patients had a history of documented or suspected Aspergillus (n = 11) or Candida (n = 1) pneumonia. The patient with preceding Candida pneumonia died from systemic infection by Candida krusei and one other patient died from relapsing Aspergillus

TABLE IIIB Maximum values for laboratory parameters under therapy with liposomal amphotericin-B compared to the start level prior to the onset of the drug. Given is the base level prior and the maximum value under therapy with liposomal amphotericin-B (median, range in brackets).

Parameter	Prior to Onset	Maximum Under Therapy
creatinine	1,0 (0,2–3,5)	1,4 (0,4–4,2)
bilirubin	1,5 (0,2–2,6,9)	2,5 (0,2–70,8)
OT	7 (3–46)	29,5 (5–662)
PT	19,5 (3–221)	41 (6–1837)

TABLE IV Course of Aspergillus and Candida antigene in sera under treatment with liposomal amphotericin-B

Course	Aspergillus	Candida
decrease	0	5
no change	2	21
always negative	66	32
increase	6	16

A significant change of titre requires at least two steps, e.g. from 1/8 to 1/32. A positive serology for Aspergillus requires at least a titre of 1/2, and a positive Candida-serology a titre of 1/4.

TABLE V Culture-Positive Patients

P	Age (y)	Sex	Dx	BMT	Mm	H	Fungus-Prophyl	VOD	GvHD	Clinics	C-ag	Asp-ag	Fungus Source	Fungus Species	Conv Am-B (Days)	lip Am-B (Days)	Start Am-B (mg/kg)	End Dose (mg/kg)	Outcome	Follow-up from bmt	n/e
1	51	m	AML	mud	0	A	Itraconaz Am-Bn	y	0	pneumonia sepsis	8	4	BAL blood	Asp. fum.	3	9	3	5	death	14	21/n
2	27	m	ALL	allo	0	0	Fluconaz	n	3	sepsis	8	0	blood cathether	C. lambica	4	18	1	3	cr	6	31/y
3	39	m	ALL	allo	1	C*	Fluconaz	y	3	pneumonia sepsis	4	0	BAL blood urine	C. krusel	1	11	2	3	death	21	26/n
4	19	f	ALL	mud	0	0	Fluconaz	n	1	penumonia sepsis	4	0	blood	C. glabrata	0	5	3	5	death	36	39/n
5	28	m	SAA	allo	0	0	Fluconaz	n	0	sinusitis pneumonia sepsis	4	8	sinus blood	Asp. flavus	1	18	3	5	death	21	29/n
6	39	m	MPS	allo	0	0	Itraconaz	y	2	penumoania sepsis	8	2	BAL blood stool urine catheters	C. krusel	27	16	4	4	death	33	43/n
7	14	f	MLD	mud	0	0	Fluconaz	n	3	pneumonia sepsis	64	0	BAL blood stool urine	C. krusel	5	40	2	3	death	54	18/y
8	39	f	2nd AML	allo	0	0	Itraconaz AM-B-o+n	n	0	pneumonia	0	0	BAL	Asp. fum.	0	9	3	3	death	19	20/n
9	48	m	ALL	allo	0	0	Itraconaz	n	1/c	pneumonia	8	0	BAL	C. krusel C. glabrata	11	23	5	3	death	349	15/y
10	32	f	AML	allo	0	0	Itraconaz Am-B-o+n	y	3	sinusitis pneumonia	1	8	sinus	Asp. fum.	6*	44*	3	5	death	62	28/y
11	32	f	CML	alpb	0	0	Itraconaz Am-B o+n	y	3	pneumonia	0	8	BAL	Asp. fum.	6	4	2	5	death	101	10/y

Abbreviations used in table 5: Fluc.: Fluconazole, Itra.: Itraconazole, mm: mismatches, H: history of mycosis under preceding therapy (0 = none, C = candidosis, A = aspergillosis, *:suspected), GvHD = Graft versus host disease (0–1°: no steroids were given, 2°: 2mg/kg methylprednisolone, 3–4°: initially 20mg/kg methylprednisolone for 3–4 days followed by gradual tapering, please refer to the text, c: chronic GvHD), VOD: veno-occlusive disease, C-ag: Candida antigen titre 1/x, Asp-ag: Aspergillus antigen titre 1/x, BAL: bronchoalveolar lavage. n/e = engraftment/duration of neutropenia < 1000/µl (days),[*]: Patient #7 had prior to her death signs of a secondary engraftment failure.

pneumonia. There was no evidence for recurrent Aspergillosis in the other 10 patients.

The response of fever to liposomal amphotericin-B was evaluable in 60 patients. In 29/60 patients, temperature decreased below 37,5°C, in 31/60 patients, temperature did not respond to antimycotic therapy with liposomal amphotericin-B. Temperature curves of 14 patients could not be evaluated, because temperature decreased under preceding antibiotic therapy or under therapy with conventional amphotericin-B prior to the switch to the liposomal formulation.

At a median follow-up of 29 (13–143) days after transplantation, 52 patients have been discharged from the BMT-unit without any evidence for fungal infection. 10 patients have died from deep or systemic mycosis, one women died of computed tomography documented cerebral aspergillosis, and 11 patients have died from severe GvHD (n = 5), therapy related toxicity (n = 3), and non-fungal infection, relapsing leukaemia, or cerebral bleeding (n = 3).

4. DISCUSSION

74 patients undergoing allogeneic or autologous bone marrow or blood stem cell transplantation were treated with liposomal amphotericin-B for suspected or documented mycosis. 10/11 patients with culture documented mycosis died from their infection. Additionally, a woman with cerebral aspergillosis documented by computed tomography with rising Aspergillus-antigen died from her infection of the CNS, unfortunately the diagnosis could not be confirmed by histology because an autopsy was not permitted. A man with Candida lambica sepsis was cured from his infection by liposomal amphotericin-B. None of the remaining 62 patients including 34 patients with serologic evidence for invasive aspergillosis or candidiasis developed deep fungal infection. 11 patients died from therapy related toxicity, non-mycotic infections and other complications. 52 patients have been discharged from the BMT-unit without evidence for deep mycosis.

Deep or systemic mycoses still remain a major infectious problem in immunocompromised patients. In an autopsy study, fungi have been responsible for 28% of deaths in patients with haematologic malignancies.[1] Patients undergoing myeloablative high-dose therapy are highly susceptible to bacterial and mycotic infections due to complete aplasia. In the allogeneic setting, the risk for fungal and viral infections is further increased by immunosuppression, immunologic differences and complications such as GvHD.[2] In bone marrow transplant recipients, even suspected fungal infection requires immediate broad spectrum antimycotic therapy. Successful treatment of systemic mycosis is difficult, even in patients *treated* by standard antineoplastic therapy. 9/11 of our patients with culture-documented mycoses had increased risk for systemic infections due to hepatic injury because of veno-occlusive disease (n = 1), acute or chronic GvHD under steroid therapy (n = 3), and matched-unrelated-donor-grafting (n = 1) alone or in combination (n = 4). Several investigators have described the favourable outcome of patients with culturally proven mycoses after treatment with liposomal amphotericin-B.[17] Recently, Chopra *et al.* described curing of 7/9 patients with culture-positive Aspergillosis (n = 6) and Candidiasis (n = 3).[18] All patients had underlying haematologic disease, but it was not specified if allogeneic BMT has been performed in any of these patients. Furthermore, the outcome in relation to the fungal species was not given. Mills *et al.* have treated 116 patients with liposomal amphotericin-B and cured 2/3 patients with documented aspergillosis after allogeneic bone marrow transplantation.[17] Unfortunately, we cannot confirm these encouraging results. However, it should be mentioned that 9/11 our patients died from aspergillosis or candidiasis, had additional severe organ impairment or underwent intensive steroid therapy for graft-versus-host disease. Thus, the comparison of our culture-positive patients with culture-positive patients described by other investigators might be difficult by because of their very high risk status. One could say, that the percentage of culture-positive patients in our collective series could have been increased by employing more invasive techniques like open or transbronchial lung biopsy or by more frequent or repeated broncho-alveolar lavage, but patients under-

going bone marrow transplantation have an increased risk for bleeding and haemorrhage due to neutropenia and thrombopenia as well as for bacteriaemia induced by endoscopy. Therefore, our patients with proven mycosis might represent a group with very advanced disease who are indeed incurable.

The prevention of recurrence of aspergillosis by liposomal amphotericin-B was favourable in our series. Only one of 11 subjects with a history of documented or suspected aspergillosis developed a relapse of his mycosis under transplantation and died from Aspergillus fumigatus pneumonia.

We confirm the very low incidence of adverse effects of liposomal amphotericin-B as reported by other investigators.[11] In only one case was the withdrawal of the drug necessary due to chills and fever. The median increase of creatinine under at median 13 days of antimycotic therapy was 1,4 mg/dl which is still the upper normal value and the creatinine remained stable or decreased in patients after an increase under preceding therapy with conventional amphotericin-B. In 77% of our patients, the creatinine did not increase to 150% compared to the base line prior to the onset. The potential hepatotoxicity of liposomal amphotericin-B is difficult to evaluate, nevertheless, the median maximal increase of bilirubin was 2,5mg/dl compared to the base line value of 1,5mg/dl. It should be pointed out, that bilirubin may increase dramatically during GvHD and that 65% of our patients with increasing bilirubin had GvHD ≥ 3°.[2,19] Even prolonged therapy up to 55 days was well tolerated.

There are some hints, that the in-vitro activity of liposomal amphotericin-B against yeasts may be slightly decreased compared to the conventional formulation. We have determined the minimal inhibitory concentrations of conventional and liposomal amphotericin-B to Candida strains cultured from our patients and found, that MIC's of liposomal amphotericin-B were between 1 and 3 titre steps higher compared to the conventional drug for clinical isolates as for ATCC reference strains.[20] Susceptibility testings published comparing MIC's of both preparations gave controversial results and the susceptibility of yeasts to liposomal amphotericin-B seems to depend on the lipids used.[14] Karyotakis *et al.* compared conventional and liposomal amphotericin-B in an animal study and found that for treatment of experimental Candida krusei infections 2mg/kg of conventional and 8mg/kg of liposomal amphotericin-B[15] had comparable activities.

We conclude, that treatment of systemic fungal infections in marrow recipients remains still a problem, even under therapy with liposomal amphotericin-B. Favourable toxicity of the liposomal preparation in patients undergoing standard antineoplastic chemotherapy as well as myeloablative high-dose therapy followed by autologous or allogeneic bone marrow transplantation together with the in-vitro data cited above should encourage investigators to study efficacy and side effects of increased doses of liposomal amphotericin-B up to at least 8mg/kg and to compare these results with those obtained with the standard drug in randomised studies. Furthermore we conclude, that efficacy of antifungal treatment in marrow recipients is difficult to compare with results obtained in patients treated with non-myeloablative chemotherapy without additional immunosuppression. Additional risk factors of BMT-patients should be specified more detailed in future reports.

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