BACTEREMIA AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION : INCIDENCE AND PREDICTIVE VALUE OF SURVEILLANCE CULTURES

Running title: Bacteremia after BMT

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SUMMARY

We studied 622 transplants between 1982 and 2001 to (1) determine the incidence, timing and etiology of bacteremias, and (2) examine the ability of routine surveillance cultures to predict bacteremias. A total of 404 episodes (0.65 episode per patient) occurred in 248 patients, due to coagulase-negative staphylococci (n=171, 42%), gram-negative bacteria (n=129, 32%), streptococci (n=48, 12%), other gram-positive bacteria (n=33, 8%), anaerobes (n=9, 2%) and fungi (n=14, 3%). Bacteremias were more frequent in allogeneic (0.96 episode/patient) compared to autologous (0.44) transplants ($p<0.0001$). The overall incidence decreased from 0.92 episode/patient until 1990 to 0.66 in 1991-1996 and 0.55 in 1997-2001 ($p<0.0001$), but this was only observed in autologous transplants. Among them, 212 (53%) occurred before hospital discharge and 192 (47%) thereafter. This proportion was lower for coagulase-negative staphylococci, other gram-positive bacteria and gram-negative bacteria compared to other agents ($p=0.001$). In 50% of the cases, the agent responsible for the bacteremic episode was present in routine surveillance cultures before. In conclusion: (1) bacteremias remain a frequent complication, particularly in allogeneic transplantation, even long after hospital discharge; (2) routine surveillance cultures can predict bacteremias in 50% of the cases but the practical impact of this observation is limited in view of the costs.

KEYWORDS : hematopoietic stem cell transplantation, infection, bacteremia, surveillance cultures

INTRODUCTION

Infections are one of the leading causes of complications in patients treated with high-dose chemotherapy (1,2). Bacteremias are reported in 20% of patients with neutropenic fever, and are sometimes associated with dramatic complications such as septic shock, multi-organ failure or even death (2, 3). Patients undergoing hematopoietic stem cell transplantation (HSCT) are at high risk of developing bacteremias and infections in general because of prolonged neutropenia, mucositis, graft-versus-host disease, CMV infection and indwelling catheters. Colonization with various organisms is thought to often precede the development of infections (4-8). Therefore, surveillance cultures are often performed in HSCT recipients. In addition, prophylactic antibiotics and anti-fungal agents are used to try to prevent the development of uncontrolled infections, but their value is still debated because prophylaxis clearly causes the emergence of resistant strains leading to real concerns for the treatment and survival of severely immunosuppressed patients.

Therefore, we undertook the present retrospective study in 622 HSCT recipients (1) to determine the incidence, timing and etiology of bacteremias in our patient population; (2) to examine the ability of routine surveillance cultures to predict bacteremias.

PATIENTS AND METHODS

Patients

The study population consisted in 622 transplants performed in our BMT unit between 1982 and 2001. There were 256 allografts (41%) and 366 autografts (59%). Allografts included 106 related donor bone marrow (17% of all patients) and 86 PBSC transplants (14%), as well as 55 unrelated donor bone marrow (9%), 5 PBSC (0.8%) and 4 cord blood (0.6%) transplants. Autografts included 84 BMT (13%) and 282 PBSCT (46%). There were 283 females and 339 males. Median age at transplant was 40 years,

ranging from 1 to 69 years. Patients suffered from non-neoplasic disorders (20), AML (129), ALL (59), CML (55), MDS (22), NHL (99), Hodgkin's disease (21), multiple myeloma (107), breast cancer (70) or other solid tumors (40).

Clinical management

Until engraftment, patients received chlorhexidine mouth washes, aerosolized amphotericin B, oral ciprofloxacin (500 mg bid, between 1987 and 2000), acyclovir (250 mg/m² bid) and antifungal prophylaxis with itraconazole or fluconazole. Furthermore, all patients were kept in laminar air flow rooms. Clinical examination was performed at least once a day and body temperature was measured every 3 hours. In case of fever above 38°3C once or 38°C on three consecutive measurements, empirical antibiotherapy was started with an association of piperacillin + amikacin (1982-1990), ceftazidim + vancomycin (1991-2000) or cefepim + amikacin (since 2001).

Microbiology

Routine surveillance cultures (stool, urine, sputum, nose, tongue, throat, skin, vagina or penis, anus and blood) were obtained twice weekly. Before initiation of antibiotherapy, blood cultures were drawn through each lumen of the central catheter (Hickman or Port-A-Cath) and a peripheral vein. Additional blood cultures were obtained when clinically indicated. Identification and antimicrobial susceptibility testing were performed according to the manufacturer's recommendations by using the SCEPTOR system (BD, Brussels, Belgium) in 1982-1992 or the automated VITEK system since 1993 (BioMerieux, St Louis, Mo., USA). MICs were determined and interpretative category results (susceptible, intermediate and resistant) were also routinely provided. Interpretative criteria were based on updated NCCLS (National Committee for Clinical Laboratory Standards) breakpoints. The classification into sensitive and resistant strains was done on the basis of MIC.

Definitions and data collection

The 19 years of follow up were divided into ten consecutive periods, each including about 60 patients : period 1 (1982 to September 1987, old hospital), period 2 (October 1987 (new hospital) to 1990), period 3 (1991-1992), period 4 (1993-1994), period 5 (1995-1996), period 6 (1997), period 7 (1998), period 8 (1999), period 9 (2000) and period 10 (2001).

Bacteria were classified into six categories, taking into account both their relative frequency and their biological characteristics. These categories were : (1) streptococci (including pneumococci and enterococci); (2) coagulase-negative staphylococci; (3) other gram-positive bacteria (including staphylococcus aureus); (4) anaerobic bacteria (bacteria requiring absence of oxygen for growth, including both strict anaerobes and aerotolerant bacteria); (5) gram-negative bacteria (including pseudomonas); and (6) fungi.

According to the definitions of the Infectious Diseases Working Party of the EBMT, bacteremia or fungemia were defined by the isolation of bacteria or fungi from any blood culture in the context of fever or other clinical signs consistent with infection. For coagulase-negative staphylococci, at least 2 blood cultures needed to be positive.

The total number of bacteremias and fungemias was recorded. For each episode, we investigated whether the responsible agent had been detected in routine surveillance cultures obtained before or after the date of bacteremia or fungemia. The isolates were considered identical if susceptibility testing yielded similar results. This was only possible for bacteremias or fungemias occurring within 60 days of the transplant, i.e. mostly during initial hospitalization.

RESULTS

Among the 622 transplants, 404 episodes of bacteremia/fungemia occurred in 248 patients (table 1). This represents an overall incidence of 0.65 episode by patient overall or 1.63 episode by affected patient. These included 171 episodes due to coagulase-negative staphylococci (42%), 129 to gram-

negative bacteria (32%), 48 to streptococci (12%), 33 to other gram-positive bacteria (8%), 9 to anaerobes (2%) and 14 to fungi (3%).

The incidence and type of bacteremia clearly changed during the 10 periods studied, encompassing 20 years (table 1). The overall incidence of bacteremia decreased over the years (0.92 episode/patient until 1990 vs 0.66 in 1991-1996 vs 0.55 in 1997-2001, $p < 0.0001$). Gram-positive agents outnumbered gram-negative bacteria by a margin of at least 2 : 1 throughout the study period except in the last 2 years. In particular, coagulase-negative staphylococci represented less than one-third of all episodes until 1990, then increased to more than 50% of all episodes in the years 1991-1996 before decreasing to less than 30% since 1997 ($p < 0.0001$). After decreasing from 0.28 episode/patient in the years 1982-1992 to 0.16 episode/patient during 1993-1999, the overall incidence and relative contribution of gram-negative bacteria re-increased to 0.26 episode/patient in more recent years ($p = 0.0053$). For the other agents, including fungi, no particular pattern of evolution was evident, but the number of such episodes was quite small.

Bacteremias were significantly more frequent in allogeneic compared to autologous transplants. The overall incidence of bacteremia was 0.96 episode/patient in allogeneic transplants versus 0.44 in autologous transplants ($p < 0.0001$). The incidence of bacteremias in allogeneic transplant recipients did not change over the years, whereas in autologous transplant recipients the number of bacteremias decreased since 1993 following the systematic use of PBSC as the source stem cells (1.04 versus 0.33 episode/patient, before and after 1993 respectively, $p<0.0001$).

Among the 404 episodes of bacteremia/fungemia, 212 (53%) occurred before patients were discharged from the hospital and 192 (47%) thereafter (table 2). About 48% of all episodes took place before day 30 post-transplant. For streptococci, anaerobes and fungi, 65%, 90% and 64% of events, respectively, occurred before day 30. This proportion was lower ($p = 0.001$) for coagulase-negative staphylococci, other gram-positive bacteria and gram-negative bacteria, with 44%, 44% and 36%, respectively, occurring in this early post-transplant interval. The incidence of bacteremia remained high well beyond day 100. A clear difference ($p = 0.034$) appears between allografts and autografts (table 3).

After autologous transplantation, the majority (59%) of episodes occurred before hospital discharge, i.e. essentially during the period of neutropenia. On the other hand, the opposite was true after allogeneic transplantation where only 48% of events took place before discharge.

To determine whether routine surveillance cultures were useful or not to predict bacteremias, we analyzed all episodes occurring before day 60 post-transplant to examine whether the responsible agent was detected before or after the first day of bacteremia or never (table 4). There was a total of 218 bacteremic episodes before day 60 (54%), excluding those happening in the non-myeloablative setting because no routine surveillance cultures were performed in this type of patient. In 109 cases (50%), the agent responsible for the bacteremic episode was present in routine surveillance cultures before. Otherwise, the agent was absent in most of the cases (42%) or only detected after the bacteremic event (8%). Among the various categories of agents, coagulase-negative staphylococci were the only ones to be present in surveillance cultures in advance in the majority of the cases (74%). On the contrary, streptococci, other gram-positive bacteria and anaerobes were seldom identified in previous surveillance cultures. Gram-negative bacteria (45%) and fungi (60%) were present in surveillance cultures before the infectious episode in about half of the cases. These differences are highly significant ($p < 0.0001$).

DISCUSSION

We conducted a retrospective survey on the incidence, timing and etiology of bacteremias and fungemias in recipients of a hematopoietic stem cell transplant in our unit between 1982 and 2001. A major aim of our study was to examine the ability of routine surveillance cultures to predict the causative agents of bacteremia, one of the most frequent life-threatening infections in neutropenic patients (10). Indeed, the mortality primarily or secondarily due to infections has been reported to reach 60% in some series of patients undergoing hematopoietic stem cell transplantation (11,12).

We identified a high incidence of bacteremia (404 episodes for 622 transplants). This is higher than in the majority of the studies (1-3,12-15) in which the overall incidence ranged from 20% to 62%.

This particularly high incidence could be related in part to the length of our follow up (19 years), whereas many studies only considered the early post-transplant period. In addition, the definition of bacteremia was broader in our study. First, we labeled as bacteremia any infectious episode with a positive blood culture, even if another site of infection, such as pneumonia, was also present. Second, in accordance with recent EBMT guidelines, a single (2 for coagulase-negative staphylococci) positive blood culture was considered sufficient for establishing the diagnosis. Third, for the purpose of the analysis in relation to surveillance cultures, a single episode with 2 different agents was counted as 2 separate episodes.

The total number of bacteremias decreased over time. This observation is in accordance with the literature (1-3,10,12-14,16-18) and may be related to a number of factors. These factors include a reduction in the duration of neutropenia with the more generalized use of myeloid growth factors, use of peripheral blood as the preferred source of stem cells (particularly true for autologous transplants since 1993 in our study) and a larger number of autologous transplants relative to the number of allogeneic transplants. We cannot evoke improvements in preventive strategies, as prophylactic measures for bacterial infections did not change much over time. In particular, quinolone prophylaxis was used during most of our study period (years 1987-2000, i.e. periods 2 through 9) and it is too early to know whether abandoning such prevention since 2001 will translate into any significant change in the incidence of gram-negative bacteremia. Among the 404 bacteremic episodes collected, a large number (42%) was due to coagulase-negative staphylococci but this proportion decreased after 1996. Gram-negative bacteremia represented 32% of all episodes with an increasing incidence of resistant strains in periods 9 and 10 (9). As discussed in our previous study (9), the introduction of "selective" decontamination with ciprofloxacin between 1987 and 2000 as well as the use of an association of a glycopeptide and a third-generation cephalosporin as empiric antibiotherapy may be responsible for this evolution towards more resistant Gram-negative agents.

In our experience, about half of bacteremias (48%) occurred before day 30, i.e. during neutropenia before engraftment. This was particularly true for streptococci (65%), anaerobes (90%) and

fungi (64%), whereas only 40% of bacteremias due to other agents occurred during this early post-transplant interval. Therefore, neutropenia appears to be a major risk factor for bacteremia/fungemia in our study despite the administration of fungal and bacterial prophylaxis. Other studies also point to this risk factor, although it is still the matter of some debate (1,2,12,14,16,17,19). Other possible explanations, during the first 30 days include mucositis and the presence of central venous catheters that have both been linked to the occurrence of bacteremia (1,3,10,12,15,20,21). Contrarily to autografts, allografts were more frequently associated with later bacteremias after hospital discharge and thus after engraftment (127 vs 117 events). Therefore, after allogeneic transplantation, neutropenia does not appear to be the most important risk factor. This would suggest that late bacteremias are related to persistent immunosuppression, particularly in the setting of chronic GVHD (22). Indeed, it is not surprising to observe that late bacteremias were almost exclusively encountered in recipients of an allogeneic transplant, or in patients experiencing relapse and reinduction chemotherapy.

The interest and cost-effectiveness of routine surveillance culture has always been controversial and not well established to our knowledge (4-8,23-26). Our study shows that routine surveillance cultures can predict the etiology of a bacteremia in 50% of the cases. For coagulase-negative staphylococci, the predictive value of such cultures is in fact quite low because of the very high rate of colonization observed in our patients (77%). Furthermore, routine surveillance cultures were unable to predict bacteremia with streptococci or anaerobes, which occurred mostly before day 30, the period during which we performed those cultures. Therefore, we can conclude that for these categories of bacteria, routine surveillance cultures are not useful and probably are not cost effective. However, surveillance cultures were more predictive for episodes associated with gram-negative bacteria or fungi. For fungi, surveillance cultures are mainly useful in identifying colonizing strains that could require more aggressive anti-fungal therapy, whereas fungal susceptibility testing is less predictive of clinical response to anti-fungal agents. For gram-negative bacteria, previously established sensitivities to antibiotics may be most useful in implementing successful therapy right away. In addition, we have previously observed that invasive gram-negative bacteria were overall less susceptible to antibiotics that

colonizing bacteria (9) and appropriately targeting them appears therefore critical. However, even if we take the conservative figure of 30% resistance to our standard empiric antibiotic regimen, only a very small number of gram-negative bacteremias (30% of 28 episodes = 8 episodes over 19 years, i.e. 13% of gram-negative bacteremias or 2% of all bacteremias) would be better managed with the help of surveillance cultures. This would certainly not be cost-effective.

However, an other interest of routine surveillance cultures remains that they contribute to determine the bacteriological ecology of a transplant unit and therefore enable to develop prophylactic and empirical antibiotic regimens most appropriate both to be efficient and to prevent the emergence of resistant strains. This brought about major changes of antibiotic policy in our unit (9).

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TABLE 1 : Bacteremias and fungemias according to the year of transplantation.

Transplant period	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Total**
	(1982 to 09-87)	**(10-87 to 1990)**	**(1991-1992)**	**(1993-1994)**	**(1995-1996)**	**(1997)**	**(1998)**	**(1999)**	**(2000)**	**(2001)**	
Streptococci	5	10	4	3	5	3	6	5	3	4	**48**
Coag-neg staphylococci	14	17	28	17	32	9	15	9	11	19	**171**
Other Gram-pos	6	5	3	2	6	2	3	1	3	2	**33**
Anaerobes	2	3	0	0	2	0	0	0	2	0	**9**
Gram-neg	19	11	12	10	17	11	9	7	19	14	**129**
Fungi	2	3	2	1	2	2	1	0	1	0	**14**
Total	**48**	**49**	**49**	**33**	**64**	**27**	**34**	**22**	**39**	**39**	**404**
N of patients	49	57	45	70	107	56	61	49	72	56	**622**
N/ patient	0.98	0.86	1.1	0.47	0.60	0.48	0.55	0.45	0.54	0.70	**0.65**
N of affected patients	31	28	25	24	39	16	24	15	23	23	**248**
N/affected patient	1.55	1.75	1.96	1.38	1.64	1.69	1.42	1.47	1.70	1.70	**1.63**

TABLE 2 : Bacteremias and fungemias according to timing of hospitalization and delay after transplantation.

	Discharge		Delay after transplantation						
	Before discharge	**After discharge**	**D 0-30**	**D 31-60**	**D 61-100**	**D 101-180**	**D 180-365**	**>1 year**	**Total**
Streptococci	32	16	31	3	2	2	6	4	**48**
Coag-neg staphylococci	87	84	76	19	23	22	16	15	**171**
Other Gram-pos	14	19	12	2	6	2	7	4	**33**
Anaerobes	8	1	8	0	0	0	0	1	**9**
Gram-neg	61	68	56	12	18	15	17	11	**129**
Fungi	10	4	9	1	1	0	2	1	**14**
Total	**212**	**192**	**192**	**37**	**50**	**41**	**48**	**36**	**404**

TABLE 3 : Bacteremias and fungemias in autologous and allogeneic transplants according to timing of hospitalization.

	AUTOLOGOUS TRANSPLANTS				ALLOGENEIC TRANSPLANTS			
	Before discharge		After discharge		Before discharge		After discharge	
	N	%	N	%	N	%	N	%
Streptococci	15	68	7	32	17	65	9	35
Coag-neg staphylococci	40	61	26	39	47	45	58	55
Other Gram-pos	8	57	6	43	6	32	13	68
Anaerobes	2	67	1	33	6	100	0	0
Gram-neg	25	52	23	48	36	44	45	56
Fungi	5	63	3	37	5	83	1	17
Total	**95**	**59**	**66**	**41**	**117**	**48**	**126**	**52**

TABLE 4 : Correspondence between agents responsible for bacteremias or fungemias and their detection in routine surveillance cultures (*)

	Not detected in surveillance cultures	Detected in surveillance cultures before bacteremia	Detected in surveillance cultures after bacteremia	Total
Streptococci	26	6	1	**33**
Coag-neg staphylococci	16	68	7	**91**
Other Gram-pos	12	1	1	**14**
Anaerobes	7	0	1	**8**
Gram-neg	26	28	8	**62**
Fungi	4	6	0	**10**
Total	**91**	**109**	**18**	**218**

(*) Analysis limited to bacteremias and fungemias occurring within 60 days after transplantation.