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Causes of Death in Febrile Granulocytopenic Cancer Patients Receiving Empiric Antibiotic Therapy

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Abstract—*We reviewed the causes of death of 55 granulocytopenic patients who received empiric antibiotic treatment for fever according to an EORTC cooperative protocol; 53 presented cancer and 2 aplastic anemia. Among the 55 patients, 19 (35%) deaths were attributed to infection: 16 to bacterial and 3 to fungal infections. Among the patients with bacterial infections, 12 died from septic shock, 3 from pneumonia and 1 from* Pseudomonas aeruginosa *meningitis. The most frequent non-infectious causes of death were the cancer progression (18%) and hemorrhagic complications (27%), most often cerebromeningeal in relationship to thrombocytopenia. A large number of the patients who died from infection (78%) and hemorrhage (74%) had advanced cancer with poor chances to respond to anticancer therapy.*

INTRODUCTION

INFECTION in granulocytopenic patients is a serious life-threatening complication which requires the prompt institution of empiric broad spectrum antibiotic therapy. This practice has resulted in a substantial reduction of fatal episodes, septic shock and infectious deaths [1, 2]. Nevertheless, bacterial infection remains an important cause of death in granulocytopenic patients with cancer, along with hemorrhage, cancer progression and other medical complications.

Our purpose is to analyse the lethal complications that occurred at the Institut Jules Bordet among the patients treated in the current EORTC cooperative trials of empiric antibiotic treatment and early granulocyte transfusions [3].

MATERIALS AND METHODS

All the patients at the Institut Jules Bordet with an absolute granulocyte count of $<1000/mm^3$ and a temperature of 38.5°C or higher were eligible for the empiric antibiotic trial. Patients whose fever could be clearly attributed to non-infective causes were excluded.

The eligible patients were randomized to receive a combination of amikacin and carbenicillin with or without cefazolin. In addition, the patients with poor prognosis, if granulocytes donors were available, were randomized to receive or not to receive early empiric therapy with granulocyte transfusions [3]. Prognosis was defined as being poor if a patient had more than 2 of the following 4 conditions: granulocyte count $<100/mm^3$, creatinine >1.0 mg/100 ml, platelets $<100{,}000/mm^3$, fever >39°C. Each antibiotic was dissolved in 50–100 ml of 5% dextrose in water and administered intravenously sequentially over 30 min. The dosage of carbenicillin was 10 g every 6 hr, amikacin 500 mg every 12 hr and cefazolin 1 g every 6 hr. The antibiotic dosage was adjusted whenever renal impairment was noted. A history and physical examination, chest X-ray, blood cultures, urine and any clinically relevant site and routine biological tests were obtained. The laboratory evaluations were repeated twice or more per week.

Based on the clinical course and microbiological data, each febrile episode was classified as (1) microbiologically documented infection if there were definite signs and symptoms revealing a site of infection that could be microbiologically proven by cultures or histological material; (2) clinically documented infection if there were definite signs and symptoms of infection with an

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identifiable site but without microbiological documentation of the etiologic agent; (3) possible infection if there were equivocal signs and symptoms of infection without a definable site and with negative microbiological data; or (4) doubtful infection if, in retrospect, it was believed that the febrile episode did not represent infection.

The response to the antibiotics was classified as (1) improvement if there was a lasting return of temperature to normal or to the level before infection and a resolution of all signs and symptoms without addition of other antibiotics; (2) temporary improvement if there was improvement but relapse occurred within 5–7 days; (3) failure if there was no or a minimal response to the antibiotics or if changes or additions of antibiotic therapy were required; or (4) not evaluable if the patient had a viral or fungal infection, if a protocol violation had occurred or if the episode was classified as a doubtful infection.

The antibiotics were not changed during the first 4 days of therapy unless there was microbiological evidence of inadequate coverage associated with an inadequate clinical response. After this time the antibiotics could be discontinued or changed in the patients who were not responding. Otherwise, the trial regimen was continued for at least 5 days after temperature has returned to normal.

We have reviewed here the records of all the patients who were included in this EORTC protocol at the Institut Jules Bordet and died during the same hospitalization. Autopsy permission was sought by the physician for each case and was performed if there was no opposition by the family. In this paper the prognosis of the underlying malignancy was defined as being favorable if the antitumoral chemotherapy administered to the patient had a reasonable probability of inducing a response of the neoplastic disease and as unfavorable in heavily pretreated patients with a poor chance of presenting a response.

Table 1. Types of primary disease found in the 55 granulocytopenic patients.

Leukemias	29
Pauciblastic	2
Acute non-lymphoblastic	14
Acute lymphoblastic	9
Chronic myelogenous in blastic crisis	2
Eosinophilic	1
Erythroleukemic	1
Lymphomas	6
Hodgkin's disease	1
Non-Hodgkin's lymphoma	5
Solid tumors	18
Head and neck	1
Colon	1
Lung small cell	6
Lung epidermoid	1
Breast	4
Glioma	1
Ovary	1
Melanoma	1
Esophagus	1
Esteosarcoma	1
Bone marrow aplasia	2

RESULTS

Of the 230 granulocytopenic patients treated in the EORTC trial of empiric antibiotics at the Institut Jules Bordet 55 died during their hospitalization. Autopsy was obtained in 30 cases (54%). The ages ranged from 20 to 77 yr, with a mean of 53 yr.

Table 1 indicates the primary diseases found in these 55 granulocytopenic patients. Twenty-nine had leukemia, predominantly acute non-lymphoblastic (14 patients) and acute lymphoblastic (9 patients); among these patients, 6 were in the first month of treatment after diagnosis of the leukemia. Six patients had lymphomas mainly of the non-Hodgkin's type, 18 presented solid tumors of various types and 2 bone marrow aplasia.

At the time of the febrile episode, the primary disease was progressing from 0 months to 10 yr. Fever occurred after 1–80 days of granulocyto-

Table 2. Classification of infections

	No. of patients (%)			
	Total	Leukemias	Lymphomas	Solid tumor
Microbiologically documented:	33 (60%)	17	2	12
with bacteremia	30 (55%)	15	2	11
without bacteremia	3 (5%)	2	—	1
Clinically documented	1 (2%)	1	—	—
Possible	5 (9%)	3	—	2
Doubtful	16 (29%)	8	4	4
Total	55 (100%)	29	6	18

Table 3. Response of granulocytopenic patients with cancer to type of antibiotic treatment

Antibiotic combinations	No. tested	No. with: improvement	temporary improvement	failure	not evaluable
Good prognosis	40				
carbenicillin + amikacin + cefazolin	26	5	1	12	8
carbenicillin + amikacin	14	—	1	9	4
Poor prognosis	15				
(a) Without granulocyte donors available:	12				
carbenicillin + amikacin + cefazolin	6	—	—	3	3
carbenicillin + amikacin	6	1	—	3	2
(b) With granulocyte donors available:	3				
carbenicillin + amikacin	1	1	—	1	—
carbenicillin + amikacin + granulocytes transfusion	2	—	—	1	—
Total	55	7	2	29	17

penia, with a mean of 7 days, not including the cases of bone marrow aplasia and the patients with pauciblastic acute leukemia. Forty-five patients had a platelet count lower than 50,000/mm^3 at the time of antimicrobial therapy.

Table 2 shows that infection was microbiologically documented in 60% (most often with bacteremia) and clinically documented in only 2%. Possible and doubtful infections represented respectively 9 and 29% of the cases. Patients with lymphoma presented most often doubtful infection (4/6) related to fever due to lymphoma.

Table 3 indicates the antibiotic regimens that the patients received according to the protocol; 40 were in the good prognosis and 15 in the bad prognosis group. Only 2 patients received empiric granulocyte transfusions. An improvement was noted in 5 patients with good prognosis and in 2 patients with poor prognosis; 2 patients with good prognosis had a temporary improvement. Failure occurred in 21 (52%) of 40 patients with good prognosis and in 8 (54%) of 15 with poor prognosis. Seventeen patients were not evaluable.

Antibiotics were started 1 hr to 2 days after the onset of fever. Seventeen patients had received nonabsorbably antibiotics; 38 were hospitalized in single rooms, 1 in strict protective isolation and others were on regular hospital wards.

Table 4 indicates the sites of microbiologically and clinically documented infections according to the underlying primary disease: oral cavity (4), skin and soft tissues (1), urinary tract (3), trachea, bronchus and lung (16), intestine and esophagus (2), nose and sinus (1), intravenous site (2) or ear (1); 4 patients had bacteremia without identification of the primary site.

Table 5 shows the pathogens isolated from the 33 microbiologically documented infections: *Escherichia coli* (9), *Staphylococcus aureus* (4), *Klebsiella* species (4), *Pseudomonas aeruginosa* (9), *Candida* species (1), Group D *Streptococcus* spp. (2), *Enterobacter* spp. (1), *Staphylococcus epidermis* (7), *Streptococcus pneumoniae* (1) and *Providencia* species (1); 5 patients had multiple pathogens.

Table 6 shows the causes of death in these 55 febrile granulocytopenic patients who received empiric antibiotic therapy. Sixteen (29%) died from bacterial infection: 12 from septic shock, 3 from pneumonia and 1 as a consequence of *P. aeruginosa* meningitis; 7 had leukemia and 9 had solid tumors. Three died from disseminated

Table 4. Sites of microbiologically and clinically documented infections

Site	Total (as a source of bacteremia)	Leukemia	Lymphoma	Solid tumors
Oral cavity	4 (3)	2 (2)	—	1
Skin/soft tissues	1 (1)	1 (1)	—	—
Urinary tract	3 (3)	—	1 (1)	2 (2)
Trachea/bronchus/lung	16 (13)	9 (6)	—	6 (6)
Intestine/esophagus	2 (2)	—	1 (1)	1 (1)
Nose/sinus	1 (1)	1 (1)	—	—
Intravenous site/catheter	2 (2)	1 (1)	—	1 (1)
Ear	1 (1)	1 (1)	—	—
Bacteremia (no primary site identified)	4 (4)	3 (3)	—	1 (1)
Total	34 (30)	18 (15)	2 (2)	12 (11)

Table 5. Pathogens isolated from the 33 microbiologically documented infections

	As a pathogen				In bacteremia				As one of multiple pathogens			
	T*	Le	Ly	ST	T	Le	Ly	ST	T	Le	Ly	ST
Escherichia coli	9	6	—	3	8	5	—	3	2	2	—	—
Staphylococcus aureus	4	1	—	3	3	1	—	2	—	—	—	—
Klebsiella spp.	4	3	—	1	4	3	—	1	3	3	—	—
Pseudomonas aeruginosa	9	4	1	4	9	4	1	4	1	—	—	1
Candida spp.	1	—	1	—	1	—	1	—	1	—	1	—
Group D *Streptococcus* spp.	2	—	—	1	2	—	—	1	1	—	—	1
Enterobacter spp.	1	—	—	—	1	—	—	—	—	—	—	—
Staphylococcus epidermidis	7	4	1	1	5	3	1	—	1	—	1	—
Streptococcus pneumoniae	1	1	—	—	1	1	—	—	—	—	—	—
Providentia spp.	1	1	—	—	1	1	—	—	1	1	—	—
Total pathogens	39	20	3	13	35	18	3	11	10	6	2	2
Total patients	33	17	2	12	30	15	2	11	5	3	1	1

T = total; Le = leukemia; Ly = lymphoma; ST = solid tumor.

Table 6. Causes of death in the febrile granulocytopenic patients treated with empiric antimicrobial therapy

	No. of patients	Leukemia	Lymphoma	Solid tumors
Bacterial or fungal infection:	19	8	—	10
septic shock	12	4	—	8
pneumonia	3	2	—	1
meningitis (*P. aeruginosa*)	1	1	—	1
disseminated fungal disease	3	1	—	1
Bleeding:	15	10	2	2
diffuse hemorrhage	6	4	2	—
cerebromeningeal bleeding	9	6	—	2
Progression of cancer	10	5	1	4
Other	11	6	3	2
renal insufficiency related to antimicrobial therapy	1	1	—	—
myocardial infarction	2	1	—	1
intestinal perforation	1	—	1	—
carcinomatous meningitis	1	—	1	—
interstitial lung disease	1	—	1	—
hyperkalemia	1	—	—	—
hypokalemia	1	1	—	—
acute pulmonary edema	2	2	—	—
anemia	1	1	—	—
Total	55	29	6	18

fungal disease. Fifteen patients (27%) died of diffuse hemorrhage (6 patients) or cerebromeningeal bleeding (9 patients); 10 presented leukemia, 2 had lymphomas, 2 solid tumors and 1 aplastic anemia. The other deaths were caused by non-infectious complications: renal insufficiency related to antimicrobial therapy (1), myocardial infarction (2), intestinal perforation (1), carcinomatous meningitis (1), interstitial lung disease of unknown etiology (1), hyperkalemia (1), hypokalemia (1) or acute pulmonary edema (2). One patient was a witness of Jehovah who refused blood transfusion; he died from severe anemia.

Table 7 shows the principal causes of death according to the actual prognosis of the underlying malignancy. Most of the patients had very advanced disease, having received all known effective treatments before their present admission. Actually, only 22% (4/19) of the patients who died from infection and 26% (4/15) of those who died from hemorrhage were treated with a reasonable probability of obtaining a remission of the neoplastic disease; all these patients presented a leukemia. The majority of the deaths occurred in patients with very unfavorable prognosis because of their advanced neoplastic disease and the lack of active therapeutic regimens.

Table 8 gives the characteristics of the 12 granulocytopenic patients who died from septic shock. The causative pathogens, whose sensitivity to the antibiotics is indicated in the table, were *E. coli* (3), *Klebsiella* spp. (2), *Pseudomonas aeruginosa* (5) and Group D *Streptococcus* spp. (2). Two patients had mixed infections (*E. coli* + *P. aeruginosa* and *P. aeruginosa* + Group D

Table 7. Causes of death according to the prognosis of the underlying malignancy

Causes of death	Prognosis								Total
	Favorable				Unfavorable				
	T	Le	Ly	ST	T	Le	Ly	ST	
Infection	4	4	—	—	14	4	—	10	18
Hemorrhage	4	4	—	—	10	6	2	2	14
Cancer progression	0	—	—	—	10	5	1	4	10
Total	8 (19%)				34 (81%)				42 (100%)

T = total; Le = leukemia; Ly = lymphoma; ST = solid tumors.

Table 8. Characteristics of the 12 granulocytopenic patients who died from septic shock

Patient No.*	Pathogen(s)	Sensitive to: amikacin	carbenicillin	cefazolin
1. (ST)	*P. aeruginosa*	S	R	R
	Group D *Streptococcus*	R	S	R
2. (ST)	Group D *Streptococcus*	R	S	S
3. (ST)	*Klebsiella* spp.	S	R	S*
4. (ST)	*P. aeruginosa*	S	R	R*
5. (ST)	*P. aeruginosa*	R	R	R*
6. (Le)	*Klebsiella* spp.	S	R	S*
7. (Le)	*E. coli*	S	S	S
8. (Le)	*P. aeruginosa*	S	R	S*
9. (Le)	*E. coli*	S	R	R*
	P. aeruginosa	S	R	R*
10. (ST)	*E. coli*	R	R	S
11. (ST)	No pathogens isolated			
12. (ST)	No pathogens isolated			

*Cefazolin administered to the patient (all received amikacin and carbenicillin).
LE = leukemia; ST = solid tumor.

Streptococcus); in 2 other patients no pathogens were isolated. All but one of these patients were treated with at least 1 effective antibiotic but only 4 were treated with active combinations of antimicrobials.

The initial site of infection was the oral cavity (1), the trachea, bronchus or lung (5), the intestine and esophagus (1), the nose and sinus (1) or an intravenous site (1); 2 patients had bacteremia without an obvious site. Four had leukemia and 8 solid tumors. In these 12 patients antibiotics were given 1–24 hr after the onset of fever, most often 2 hr. Four had received prior prophylaxis with oral non-absorbable antibiotics and 8 were in single rooms. One had a granulocyte count $<100/mm^3$, 6 between 100 and 500 and 5 over 500. Eight patients died during the 24 hr after the onset of antimicrobial treatment; the others after 7, 8, 9 and 21 days with uncontrolled infection.

DISCUSSION

This review of 55 febrile granulocytopenic patients who died after receiving empiric broad-spectrum antibiotic therapy at the Institut Jules Bordet reveals that 19 (35%) died directly from the infectious process: 16 (29%) died of bacterial and 3 (5%) of fungal infections. The initial febrile episode requiring empiric antimicrobial therapy in those patients who eventually died could be microbiologically documented in 60% of the patients studied here, most of whom had bacteremia. This is a higher incidence of bacteremia than usually observed in a population of febrile granulocytopenic patients requiring empiric antibiotic therapy, most of whom will survive [4].

It should also be stressed that most of these patients who eventually died did not respond satisfactorily to the empiric antibiotic therapy.

The 2 other important causes of death were hemorrhagic complications (27%), mostly cerebromeningeal, and cancer progression (18%). It should be stressed that for the leukemic patients bleeding appeared to be the first direct cause of death (35 vs 17% for solid malignancies).

In other studies on the causes of death in patients with cancer [5–7] or with acute non-lymphocytic leukemia [8], infection was found to be the direct cause of death in 10–50% of the patients, the latter being a figure similar to our findings. Infection as a cause of death appeared to be related to the degree of bone marrow depression and to the extension of the underlying disease. Hemorrhagic fatal complications were directly related to thrombocytopenia; in our series 82% of

the patients had a platelet count lower than 50,000/mm^3 at the time of empiric antimicrobial therapy. Increasing low platelet counts by early platelet transfusions therefore seems to be a necessity to avoid these hemorrhagic complications [9].

In a previous study from this center, cancer progression was the cause of death in about 20%; this is very similar to the present results. Moreover, a large number of the patients who died from infection or hemorrhage in this study had an unfavorable prognosis. They suffered from far-advanced neoplastic disease, particularly in the group of patients with solid tumors who had previous multiple antitumoral treatments.

Cancer progression and no available effective therapy seemed to represent the main factor of unfavorable prognosis in febrile granulocytopenic patients receiving empiric antimicrobial therapy.

Our data show that septic shock was the most frequent cause of infectious death in febrile granulocytopenic patients. Septic shock was present in two-thirds of our cases at the time when the antibiotics were started and it developed during antibiotic therapy in the other one-third as a result of uncontrolled bacterial infection. These data suggest that in granulocytopenic patients bacterial infection remains the major cause of death despite the early institution of empiric antimicrobial therapy. Since septic shock was present in most patients, attention to and early therapy of vasomotor collapse seems to be indicated under these circumstances.

Moreover, our analysis shows that only 4 out of the 12 patients who died with septic shock were treated with active combinations of antimicrobials. Clinical and experimental data [10] suggest that synergistic combinations of drugs should be used as empiric therapy in severely neutropenic patients. The routine use of synergistic combinations might lead to better results in the treatment of septicemia with shock in these compromised hosts.

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