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ORIGINAL ARTICLE

A prospective study of febrile neutropenia in lung cancer patients

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ABSTRACT

BACKGROUND There are few data on microbiology of febrile neutropenia (FN) in lung cancer patients. The primary objective of this study was to evaluate the epidemiology of FN in this population.

PATIENTS AND METHODS All patients with lung cancer treated with chemotherapy in the Institut Jules Bordet (a cancer hospital) and who developed FN (PMN <500/mm^3) were included in the present prospective study. Febrile neutropenia was defined as any febrile episode (38.5°C once or 38.0°C twice) occurring during neutropenia (neutrophil count <500/mm^3).

RESULTS Ninety five patients, 62 with non-small cell and 33 with small cell lung carcinoma developed FN. A total of 102 FN episodes were observed. Of these, 46 were microbiologically and 14 clinically documented. The most frequent site of infection was the lung (31%). Gram-negative bacteria, mainly Escherichia coli and Haemophilus influenzae, were most commonly observed. In bacteremic patients, Gram-positive bacteria, essentially Streptococcus sp, Enterococcus sp and Staphylococcus aureus, accounted for 39% of the micro-organisms.

CONCLUSION Lung constitutes the predominant site of infection in febrile neutropenic lung cancer patients. In these patients, E. coli and H. influenzae are the most commonly documented pathogens, except in case of bacteremia where Streptococcus sp and S. aureus as well as E. coli are the principal pathogens.

KEY-WORDS: *febrile neutropenia, microbiology, non-small cell lung cancer, small cell lung cancer, epidemiology, risk factors*

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INTRODUCTION

Infection is one of the commonest complications associated with cancer. Different factors are contributing: immunosuppression related to cancer or its treatment, visceral neoplastic obstruction, use of implantable devices and invasive procedures, disruption of physiological barriers or blood product transfusion [1]. In lung cancer patients neutropenia, chronic obstructive bronchopulmonary disease (COPD) and bronchial obstruction are probably the main causes favouring infection. Epidemiological data on infections in lung cancer patients are scarce. We have previously reported a prospective epidemiological study demonstrating that the majority of lung infections were predominantly due to Gram negative bacteria [2]. Few other studies have assessed the respective frequency of the infection types and microbiology in these patients, also demonstrating that infections occur essentially in the lung.

Chemotherapy is now generally accepted as part of the treatment of patients with lung cancer, whatever stage or histology are considered [3-5]. Chemotherapy is

frequently associated with intermittent neutropenia, a factor well known to predispose to infection. Data specifically collected in patients with lung cancer are rare. In small cell lung carcinoma (SCLC), febrile neutropenia (FN) occurred in 18% to 77% of the chemotherapeutic cycles [6-9] or in 23% of the patients [10]. In non small cell lung carcinoma (NSCLC), up to 6% of the patients will develop FN during chemotherapy [11,12]. Those data were extracted from clinical trials assessing the role of chemotherapy in selected groups of patients. To our knowledge, only one study assessed both the type of infection and the microbiological nature of FN in patients with lung cancer. This is a retrospective analysis of a randomised study with primary endpoint the route of administration of empiric antibiotic therapy in FN. In this Japanese study, 35 patients developed 42 FN episodes, of which two thirds were fever of unknown origin (FUO) [13]. Among 15 documented infections, 10 originated in the lung.

The primary objective of our study was to determine the infection types and the microbiology of febrile neutropenia and the secondary objective to estimate its frequency in an unselected population of NSCLC and SCLC patients treated with conventional chemotherapy in a specific single centre cancer hospital.

PATIENTS AND METHODS

All lung cancer patients hospitalized in the Critical care Department or the Thoracic Oncology Unit of our cancer hospital were prospectively registered in this study at the time febrile neutropenia occurred. Febrile neutropenia was defined as any febrile episode (38.5°C once or 38.0°C twice) occurring during neutropenia (neutrophil count <500/mm^3). The data collected by the physicians in charge of the lung cancer patients was based on results provided by the microbiology laboratory and the infectious disease consultant. Specific data on some risk factors have been added: corticosteroid treatment, central or peripheral venous catheters, pleural or bladder catheters, mechanical ventilation, tracheotomy, and COPD. Cultures of blood, sputum, and urine as well as nose, mouth and anal swabs were systematically performed in addition to sampling from the suspected infectious site, if any.

Microbiologically and clinically documented infections were both considered. When the patient was presented with fever non responding to empiric antibiotic therapy without known site of infection or other etiology of the fever, such as drug, blood products transfusions and paraneoplastic fevers, the episode was classified as a fever of unknown origin (FUO).

Collection of urine, sputum and stool samples was performed according to standard procedures. Simple aspiration or bronchoalveolar lavage could be done during bronchoscopy. Protected sampling was not performed. Blood cultures were performed in duplicate, using the aerobic and anaerobic Bactec^R systems. Cultures were performed according to the routine procedures of the hospital laboratory. Bacteremia or fungemia were diagnosed when a potentially pathogenic organism was found in the blood culture. Coagulase-negative *Staphylococcus* or *Corynebacterium* were characterized as pathogens when they were isolated in more than one culture, from the blood plus a distinct clinically infected site, or from a clinically septic patient with an intravascular device. A positive urinary culture was considered as significant in the presence of focal (dysuria, polyuria) or systemic signs of infection. Tracheal secretion aspirations in intubated patients and sputum or tracheal aspirations in non-intubated patients were considered as positive if associated with clinical or radiological signs compatible with infection. Ear, nose, and throat (ENT) infections were considered significant when local signs of clinical infection were detected and a potential pathogen was simultaneously isolated from the mouth, the nose, the throat or the sinuses. Every effort was made to differentiate infection from colonization [14]. Clinically documented infections, principally when affecting the tracheobronchial tree and the skin, were considered significant if clinical or radiological signs were compatible with the diagnosis of infection as well as the evolution on empiric antibiotic therapy, and no other etiology could be identified. Superinfection was defined as a new infection that occurred during the 7 days following the completion of antibiotic therapy for the initial episode.

Binary variables were compared by chi square tests. A p value <0.05 was considered as statistically significant. All statistical tests were performed using the Statistica^R software.

RESULTS

PATIENTS CHARACTERISTICS

From 02/1997 to 12/2005, 1064 patients with NSCLC, SCLC or mesothelioma were followed in the clinic of Thoracic Oncology of our hospital. Among them, 776 patients received chemotherapy. The neoplastic disease was NSCLC in 637, SCLC in 127 and malignant pleural mesothelioma in 12. During this period, 95 patients developed 102 distinct episodes of febrile neutropenia. Some of them were included in a previous publication on infections in lung cancer patients [2]. The principal characteristics of the febrile neutropenic patients with NSCLC and SCLC are presented in Table 1.

The following comorbidities and/or potentially predisposing conditions were present at the diagnosis of the infectious episodes: COPD (n=19), corticosteroid therapy (n=13), peripheral venous catheter (n=20), central (n=4) or totally implantable venous catheters (n=18) and bladder catheter (n=3). Only two patients received G-CSF at the time of FN. Prophylactic antibiotics were not prescribed. Sixty-four percent of the infections occurred either at home (n=59) or were

TABLE 1. Characteristics of the 95 febrile neutropenic patients with NSCLC or SCLC.

	Non-small cell lung cancer	Small cell lung cancer
Number of patients	62	33
Age: median (range)	62 years (37-83)	66 years (43-77)
Gender: male/female	45/17	20/13
Stage	II 2 IIIA 7 IIIB 10 IV 43	Limited disease 8 Extensive disease 25

acquired within 48 hours after hospital admission (n=6). For patients hospitalized at the time of the infection, the median hospital stay before occurrence of febrile neutropenia was 10 days.

TYPES OF INFECTION AND MICROBIOLOGICAL RESULTS

Bacteremia or fungemia were documented in 18 cases (17.6% of all infectious episodes) of which 5 were of primary origin. The most frequent site of infection was the lung with 24 non-bacteremic and 8 bacteremic episodes. Other sites of infections, in decreasing order, were, digestive tract (n=8), urinary tract (n=7), head and neck (n=6) and skin (n=2). The distribution of infection types according to histology is shown in Table 2. Forty-six infections were microbiologically and 14 were clinically documented, 45% and 14% from the total of FN episodes respectively. Fever of unknown origin (FUO) was the final diagnosis in 42 cases (41%). Microbiologically documented infections accounted for 45% of the FN episodes with a total of 56 microorganisms (Table 3).

There were 7 documented polymicrobial infections. The most frequent pathogens were Gram-negative bacteria (n=39; 70%) followed by Gram-positive bacteria (n=13; 23%), fungi (n=2; 4%) and viruses (n=2; 4%). The four most frequent Gram-negative bacteria were *Escherichia coli* (n=13), *Haemophilus influenzae* (n=9), *Moraxella catarrhalis* (n=3) and *Pseudomonas aeruginosa* (n=3). *Streptococcus sp*. (n=3), *Enterococcus sp* (n=4) and *Staphylococcus aureus* (n=4) constituted the main Gram-positive bacteria. All fungal infections were due to *Candida albicans*. Two *Herpes simplex* cases were documented. When only pathogens documented in blood cultures were considered, Gram positive bacteria were observed more often (Table 4). Unexpected resistance to conventional antibiotics was infrequently found. None of the *Staphylococcus aureus* strains were resistant to methicillin. One *Acinetobacter baumanii* was considered as a multiresistant bacteria.

Infections resolved in 93 cases (91.2%). One episode was not assessable for response due to a lack of follow-up. The last 8 patients died from or during their febrile neutropenia, between less than 1 day and 13 days after the occurrence of the febrile episode. Those were four NSCLC (3 stage IV and one stage IIIB) and 4 SCLC (1 limited and three metastatic diseases) patients. Infection occurred at home in 5 cases. All presented with microbiologically or clinically documented infections except one FUO: pneumonia with (n=4) or without (n=1) bacteremia, fungemia (n=1) and typhlitis (n=1). Eight pathogens were documented: *Escherichia coli, Pseudomonas aeruginosa, Klebsiella oxytoca, Acinetobacter baumanii, Enterobacter aerogenes, Staphylococcus aureus*, *Clostridium difficile* and *Candida albicans*. Three bacteria were resistant to the initial antibiotic therapy, including the multiresistant *Acinetobacter baumanii*.

There were 11 superinfections. They included lung infections (n=3), soft tissue infection (n=1), mucositis (n=3), and

TABLE 2. Infection types according to tumour histology

Infection types	Non-small cell lung cancer (63 infectious episodes among 62 patients)	Small cell lung cancer (39 infectious episodes among 33 patients)
Bacteriemia	11 Primary origin 2 Lung 6 Digestive tract 1 Urinary 1 Skin 1	7 Primary origin 3 Lung 2 Urinary 2
Lung	21 (including 6 bacteriemia)	11 (including 2 bacteriemia)
Digestive tract	6 (including one bacteriemia)	2
Urinary tract	1 (corresponding to a bacteriemia)	6 (including 2 bacteriemia)
Head and neck	4	2
Skin	2 (including one bacteriemia)	-
Fever of unknown origin	27	15

TABLE 3. Documented pathogens according to tumour histology.

Pathogens	Non-small cell lung cancer	Small cell lung cancer	Total
Gram-positive bacteria	7	6	13
Streptococcus sp	2	1	3
Enterococcus sp	2	2	4
Staphylococcus aureus	2	2	4
Bacillus sp.	-	1	1
Clostridium difficile	1	-	1
Gram-negative bacteria	25	14	39
Escherichia coli	4	9	13
Haemophilus influenzae	8	1	9
Moraxella catarrhalis	2	1	3
Pseudomonas aeruginosa	3	-	3
Klebsiella sp	2	-	2
Acinetobacter sp	-	2	2
Other Gram negative bacteria	6	1	7
Other pathogens			4
Candida albicans	-	2	2
Herpes simplex	-	2	2
Total	32	24	56

bacteremia, colitis, sinusitis and FUO one case each. Nine microorganisms were documented *Xanthomonas maltophilia* (n=2), *Clostridium difficile, Staphylococcus aureus*, *Candida albicans, Candida glabrata* and *Aspergillus fumigatus* in one case each and two *Herpes simplex* I.

Among those patients presenting with FN, we looked for a possible association with clinical characteristics. Corticosteroid administration was not predictive of poorer outcome (16.7% versus 6.7%; odds ratio (OR)=2.5; p=0.24) and it was also not associated with an increased risk of superinfection (15.4% versus 10.1%; OR=1.52; p=0.63). Bacteremia was associated with catheter use (28.6% versus 10.0%; OR=2.86; p=0.02). A statistically significant association between COPD and lung infection was observed (52.6% versus 26.5%; OR=1.99; p=0.03). FUO occurred at the same frequency at home or during hospitalization (64.3% versus 53.3%; OR=1.21; p=0.27).

DISCUSSION

In this prospective study, we found that the principal site of infection in lung cancer patients was the lung. Among bacteremic episodes, lung accounted for 44% of the primary sites. Gram negative bacteria, mainly *Escherichia coli* and *Haemophilus influenzae*, predominated except in case of bacteremia where Gram positive bacteria were documented in 43% of the cases.

The aim of this study was to more precisely delineate the infection sites and nature of the responsible pathogens in lung cancer patients with febrile neutropenia. Few data are available on this topic. For the majority, they were extracted from retrospective analyses of prospective clinical trials assessing chemotherapy in SCLC or NSCLC [6-8,10-12]. In these studies, only the frequency of FN was documented. To our knowledge, only one Japanese study addressed retrospectively the question of site and microbiological nature of FN in lung cancer [13]. FUO was observed in two thirds of our cases and infection originated in the lung in the majority of the docu-

TABLE 4. Documented pathogens in positive blood cultures (n=18 bacteremic episodes)

	Original site of infection					
Pathogens	**Pulmonary**	**Urinary**	**Skin**	**Digestive**	**Not identified**	**Total**
Streptococcus sp	1	-	-	-	1	2
Enterococcus sp	1				3	4
Staphylococcus aureus	3	-	-	-	-	3
Bacillus sp.	1	-	-	-	-	1
Escherichia coli	-	3	1	-	2	6
Klebsiella sp	2	-	-	-	-	2
Pseudomonas aeruginosa	1	-	1	-	-	2
Acinetobacter baumanii	1	-	-	-	-	1
Vibrio non cholerae	-	-	-	1	-	1
Candida albicans	-	-	-	-	1	1
Total	10	3	2	1	7	23

mented FNs. Five pathogens were documented, precluding any meaningful interpretation. The present study being the larger reported, confirms that lung is the primary site of infection in most patients. We made the same observation in a previous study assessing infection in an unselected population of patients with lung cancer [2]. The high prevalence of lung as the primary site of infection, as it is suggested in our present and previous study, may be related to frequent existence of concomitant COPD, which is known to predispose to lung infections as well as to neoplastic obstruction.

We found that the predominant pathogens, in this population not receiving antibiotic prophylaxis, were Gram-negative bacteria except for bacteremia where Gram-positive bacteria were documented in 2/5 of the cases. This observation is well in accordance with observations in the recent literature in various cancer populations [15], where up to 60% of the microbiologically documented FN episodes were due to Gram-negative bacteria. Among those, *Escherichia coli* was the commonest pathogen, as it was observed in our study. Nevertheless, in our population of lung cancer patients, we found that *Haemophilus influenzae* was nearly as common as *E. coli*. This is not surprising as we made the same observation in a previous study [2] and because *H. influenzae* is a common lung or bronchial pathogen in COPD patients. Interestingly, we found that *Streptococcus sp, Enterococcus sp* and *Staphylococcus aureus* accounted respectively for 8.7%, 17.4% and 13.0% of the microorganisms documented in case of bacteriemia. An increasing frequency of *Streptococcus sp*, principally of the *viridans* group, and *Enterococcus sp* was reported in FN patients [15]. However, the increase in Gram-positive bacteremia was also due to coagulase-negative *Staphylococci* that were not documented in our study. This could be explained by the low rate of totally implantable catheters used in our daily practice, a main risk factor for bacteremia as it was found in our study.

Our observation has direct implications in clinical practice. As with FN occurring in other cancer populations, broad spectrum antibiotics must be administered in lung cancer patients on an empirical basis. Guidelines have been published by the Infectious Disease Society of America (IDSA) for the use of antimicrobials in patients with cancer and FN [16]. Outside of local epidemiology, broad spectrum β lactams or carbapenems are suggested as first-line therapy while glycopeptides must be administered only in case of documented resistant Gram-positive infection or clinical signs suggesting infection with resistant Gram-positive organisms. Oral antibiotic therapy should be considered for low risk patients. The role of new fluoroquinolones with increased activity against Gram-positive pathogens remains to be validated in randomised trials. According to the type and microbiological nature of infections and the drug-sensitivity pattern observed in our study, we suggest to use the recommendations of the IDSA in febrile neutropenic lung cancer patients.

CONCLUSIONS

In conclusion, we have demonstrated that most of the documented febrile episodes in neutropenic lung cancer patients originated from lung. Gram-negative bacteria, mainly *Escherichia coli* and *Haemophilus influenzae*, were the predominant microorganisms except in case of bacteremia, where Gram-positive bacteria were more often documented. We did not observe a higher rate of resistance to conventional antibiotics than it was expected. In lung cancer patients with febrile neutropenia, the guidelines proposed by the IDSA should be applied. Broad spectrum β lactams or carbapenems can be suggested as first-line therapy. Oral antibiotic therapy should be considered in low risk patients.

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