

Pneumonia as a cause of death in patients with lung cancer

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Background. Lung cancer is a very serious clinical problem in departments of pulmonary diseases. In many patients with lung cancer pneumonia is a secondary cause of death, which is caused not only by the progression of the disease but also by the applied treatment negatively influencing the immunity of human organism. Clinical and radiological symptoms of the infection can frequently suggest the progression of neoplastic disease. That is why in each case of deterioration of the state of patients with lung cancer the proper diagnosis of the cause should be endeavoured in order to implement the right therapeutic procedures.

Patients and methods. We have retrospectively evaluated 70 patients who died in the period between 1997 and 1999 in our Department due to lung cancer. Both clinical and bacteriological analyses of deaths were performed and a particular interest in pneumonia as a cause of death was taken.

Results. Pneumonia was diagnosed in 41 patients with lung cancer (58.5%) and *Streptococcus pneumoniae* was the main etiological factor of pulmonary infection. In patients with SCLC, the extent of inflammatory changes on chest X-ray and white blood cell count correlated negatively with the period of hospitalisation ($R = -0.6$ and $R = -0.54$; $p < 0.05$, respectively).

Conclusions. Lung cancer was the main cause of death in patients died in the Department of Tuberculosis and Pulmonary Diseases, Medical University of Łódź. Pneumonia was diagnosed in 58.5% as a secondary cause of death in lung cancer patients.

Key words: lung neoplasms; pneumonia - mortality

Introduction

Lung cancer is the most common malignant tumour in men in Poland, with the morbidity

index of about 50 in 100,000, and in women it is the fourth most common in respect of the frequency of occurrence (the morbidity index is about 8 in 100,000). All together every year about 20,000 new cases of the disease are recorded, and at the same time about 18,000 people die of lung cancer (in 1990 the number of deaths amounted to 19,301, and in 1998 to about 17,000 with the average death rate of 44.2).^{1,2}

The main causes of death in patients with lung cancer are local progression of the disease, metastases to remote organs and the

Received 7 May 2003

Accepted 21 May 2003

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This work was supported by grant 502 11 572 (135) from Medical Academy of Łódź.

respiratory system infections.^{3,4} Infections are the most frequent complications that break out by the treatment in this group of patients. The occurrence of infections is related to the immunological disorders connected with neoplastic disease, its location and progression as well to antineoplastic treatment. Among the factors favouring the respiratory system infections are mainly the ones, which are evoked by the presence of neoplasm in the respiratory system and its metastases to other organs.

The microorganisms responsible for infections in lung cancer patients may be bacteria, viruses, fungi and protozoa.^{2,5} There have even been recorded some cases of infection caused by nemathelminthes. A patient with impaired immunity is primarily (by neoplastic disease) and secondarily (by the treatment) is exposed to the infection with pathogens and also with saprophytes (opportunistic infections).^{6,7}

The aim of this research was a retrospective clinical and bacteriological analysis of deaths in lung cancer patients treated in the period between 1997 and 1999 in the Department of Tuberculosis and Pulmonary Diseases at the Medical University of Łódź, taking a particular interest in pneumonia as a cause of death.

Material and methods

The extent of the advancement of neoplastic disease was estimated on the basis of the physical examination, chest radiographs, chest and brain computed tomography, bronchofibroscope and ultrasonographic examination of the abdominal cavity. Pneumonia was diagnosed on the basis of the following criteria: increased cough, purulent sputum, dyspnoea, increase in body temperature, rise in WBC (white blood cell count) and the occurrence of new infiltrates in chest radiographs.

A microbiological examination of the sputum was performed according to the Mulder-Lanyi method.^{8,9} The sputum was collected into the Petri container in the morning, after washing of the mouth with water. This material was immediately sent to the Laboratory Department. Before the examination the sputum is 3-5 times washed by sterile 0.9% NaCl and the pus flakes are separated. Two preparations were made: Pappenheim for the cytological examination and Gram for the bacterioscopic one. Then the culture was performed and antibiotic sensitivity was denoted. The criteria of the infection covered: cytological examination, contents of eosinophils, Gram stain and culture.

Patient's characteristics

The total of 116 patients who died in the Department of Tuberculosis and Pulmonary Diseases at the Medical University of Łódź in the period between 1997 and 1999 were examined retrospectively. The primary cause of death in 70 of them (60%) was lung cancer (23 women, 47 men). As for the rest of patients the cause of death was COPD (25%), and a few others, such as tuberculosis, pulmonary fibrosis, pulmonary embolism, circulatory failure (15%). Fifty-one patients (73%) with lung tumour were diagnosed histologically: small cell lung cancer (SCLC) was diagnosed in 15 patients (6 women, 9 men), and non-small cell lung cancer (NSCLC) in 36 (5 women, 31 men). In 19 patients (12 women, 7 men) the type of neoplasm was not determined, and the diagnosis was given on the basis of the cytological examination of the sputum or bronchoscopic specimens (diagnosis: neoplastic cells). The average age of patients was 64.8 ± 11.8 years (SCLC: 62.8 ± 11.5 ; NSCLC: 63 ± 11.4). The extended disease (ED) was diagnosed in 13 (87%) patients with SCLC, the limited disease (LD) in 2 (13%). In the group with NSCLC the occurrence of metastases was detected in 12 patients (33%): clinical stage IV, and the rest of

patients were classified as stage III B. The mean disease period was 8.9 ± 4.6 months (median: 9 months) (SCLC: 8.6 ± 3.7 vs. NSCLC: 10.4 ± 4.8 ; $p > 0.05$) and the average hospitalisation period was 7.8 ± 4.6 days (SCLC: 7.1 ± 4.3 ; NSCLC: 8.4 ± 4.8). All patients were smokers and the mean cumulated cigarette consumption was 40.9 ± 18.8 pack-years (SCLC: 37.0 ± 23.0 ; NSCLC: 41.6 ± 19.7).

The basic method of the treatment in patients with SCLC is chemotherapy. PE (cisplatin and etoposide in six 3-day courses every 21 days) was the most often applied scheme among the examined patients ($n=7$). Not all the patients were given the full scheme ($n=5$) considering the lack of response or fairly large intensification of side effects. Alternatively the scheme CAV (cyclophosphamide, adriablastine and vincristine) was applied ($n=2$). In LD SCLC patients chemotherapy was supplemented with radiotherapy. The patients with NSCLC were covered by the palliative care. All patients received glucocorticoids (prednisone 20 mg/day).

Statistical analysis

The results were presented as an average value \pm a standard deviation. Statistical differences were determined with the t-test or Kolmogorov-Smirnov test. Survival curves were constructed according to the Kaplan-Meier method and differences in the survival were compared with the log-rank test. Correlations were expressed as Pearson's or Spearman's coefficient depending on data

distribution. A p value of < 0.05 was considered significant.

Results

Pneumonia was diagnosed as the secondary cause of death in 41 patients (58.5%). In the radiographs inflammatory changes occupy 3.4 ± 1.4 lung fields on average. In the blood examination no considerable changes were observed except the increased WBC (Table 1). There were no differences between measured routine panel blood parameters in SCLC and NSCLC patients.

The bacteriological diagnosis was given only in 6 patients (all with NSCLC) with pneumonia (8.5%) and Streptococcus was the most common evoking factor (Table 2).

All the patients with a diagnosed infection were subjected to the antibiotic therapy. The most frequently applied drugs were cephalosporins of II and III generation ($n=15$; 36.6%) and amoxicillin with clavulanic acid ($n=6$; 21.9%).

The autopsy was conducted in 4 patients (5.7%). In each case pneumonia was confirmed as a secondary cause of death.

Table 2. Bacteriological examination in patients with lung cancer and pneumonia

Etiologic agent	Number of patients	(%)
Streptococcus sp.	3	50
Proteus sp.	2	33
M. tuberculosis	1	17
Total	6	100

Table 1. Blood examination in patients with lung cancer and pneumonia

	Lung cancer (mean)	NSCLC	SCLC
Erythrocytes ($10^6/\mu\text{l}$)	4.4 ± 0.9	4.5 ± 0.9	3.9 ± 0.9
Hb (g/dl)	12.4 ± 2.6	12.5 ± 2.8	11.6 ± 2.8
Htc (%)	38.2 ± 7.8	38.5 ± 8.5	35.5 ± 8.3
MCHC (g/dl)	32.4 ± 0.9	32.4 ± 0.9	32.5 ± 1.1
Leucocytes ($10^3/\mu\text{l}$)	12.2 ± 7.0	13.1 ± 6.9	12.2 ± 8.4
Thrombocytes ($10^3/\mu\text{l}$)	294.5 ± 168.5	332.5 ± 180.0	236.8 ± 141.9

The survival median in the examined group was 9 months (Figure 1). For patients with SCLC it was 8 months, and with NSCLC 12 months ($p > 0.05$). The correlation analysis of the examined parameters indicated that in the group of patients with SCLC the period of hospitalisation correlated negatively to WBC ($R = -0.54$; $p < 0.05$) and the extent of inflammatory changes on radiological pictures ($R = -0.6$; $p < 0.05$) (Figure 2). In the same group of patients the positive correlation between the extent of inflammatory changes on chest x-ray and WBC was found ($R = 0.68$; $p < 0.05$).

The local progression of lung cancer ($n=20$) or the circulatory failure ($n=9$) were the cause of death in the rest of the patients.

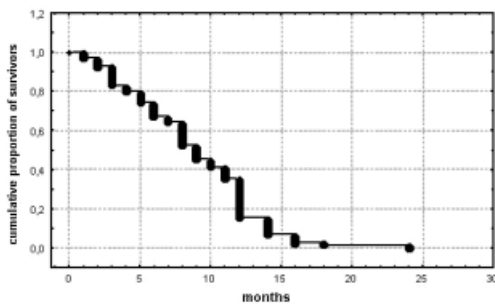


Figure 1. Survival in patients with lung cancer.

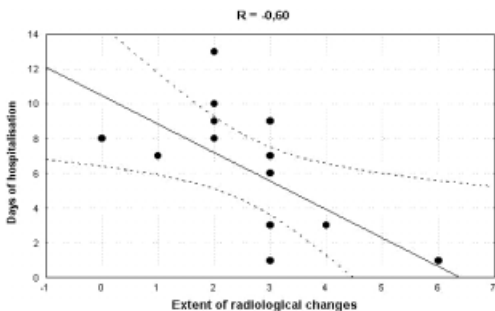


Figure 2. The negative correlation between the period of hospitalisation and the extent of inflammatory changes on chest x-ray ($R = -0.6$; $p < 0.05$) in patients with SCLC.

Discussion

During the examined period in the Department of Tuberculosis and Pulmonary Diseases of the Medical University of Łódź the most common primary cause of death was the lung cancer (60%). It is estimated that about 75-80% of all patients with lung cancer are patients with the diagnosis of NSCLC, while 20-25% are patients with SCLC.^{1,3} Similarly, in the examined group of patients the microcellular form of cancer was diagnosed in 21.4% of patients, while the non-microcellular form - in 51.4%. In the remaining patients (27.2%) the histopathological diagnosis was not made. The reason was often the short observation time of patients.

In the examined group of patients pneumonia was the main or accessory cause of death in 41 patients (58.5%). The conducted autopsy examinations in each case confirmed the clinical diagnosis. According to Remiszewski *et al.* in a group of patients with SCLC the infections of the respiratory system were the main cause of death only in 4.6% of patients, and the accessory cause in 9.1%.⁶ In examinations conducted by Putinati *et al.* the frequency of occurrence of infections in lung cancer patients was estimated on the grounds of the results of the bacteriological examination of the broncho-alveolar lavage fluid (BALF), the presence of the infectious agent was indicated in 34.3% of patients. This result is probably underestimated because in some patients showing clinical symptoms of the respiratory system infections etiological agent was not discovered (sampling was conducted during the antibiotic therapy).¹⁰ In Japanese examinations the group of patients with lung cancer was divided into three subgroups depending on the method of treatment and the frequency of the inferior respiratory tracts was estimated at 41.7-60.5%. Most often infections appeared in the group of patients receiving cytostatics and glucocorticoids.¹¹

In patients with granulocytopenia, apart from the typical for the respiratory system infections caused by alpha-haemolysing *Streptococcus*, *Streptococcus* from the D group, *Staphylococcus aureus* and *epidermidis*, *Haemophilus influenzae*, the important role is played by Gram-negative bacteria: *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Enterobacter*, *Proteus*. Subjects with the cell-mediated immunity disorders are exposed to infections caused by: *Listeria monocytogenes*, *Salmonella*, *Mycobacterium*, *Nocardia asteroides* and *Legionella*.^{12,13}

The most frequently occurring virus infections include the ones caused by: *Varicella-zoster*, *Herpes simplex*, *Cytomegalovirus* and *Ebstein-Barr virus*.^{13,14}

Other severe infections are the ones caused by fungi: *Pneumocystis carinii*, *Cryptococcus neoformans*, *Aspergillus fumigatus*, *Candida albicans*, *Candida krusei*, *Histoplasma capsulatum*, *Candida glabrata*, protozoa (*Toxoplasma gondii*). Infections caused by *Strongyloides stercoralis* were also observed.^{7,15-18}

The conducted bacteriological examinations showed that the etiological agents of pneumonia in the examined group were bacteria of *Streptococcus* and *Proteus* species as well as *Mycobacterium tuberculosis*. *Putinati et al.* indicated Gram-negative rods as the most frequent cause of infections (most often *Haemophilus sp.*) - 45.2%, Gram-positive cocci (most often *Staphylococcus aureus*) - 33.3%, *Pneumocystis carinii* and *Chlamydia trachomatis* - 16.7% as well as Gram-negative cocci - 4.8%.⁸ In the Japanese examinations cited before cases of pneumonia were caused by Gram-positive bacteria in 38.4%, Gram-negative bacteria in 30.8%, and mixed bacterial flora in 30.8%.¹¹ *Remiszewski et al.* showed that the most frequent etiological agents of the infections causing death of patients with lung cancer were Gram-negative bacteria (*Klebsiella sp.*, *Pseudomonas sp.*, *Escherichia*

coli). Gram-positive bacteria (*Staphylococcus sp.*, *Streptococcus sp.*) were isolated more sparsely. In some patients infections were caused by fungi: *Aspergillus sp.*, *Candida sp.*, *Pneumocystis carinii* and *Mycobacterium tuberculosis*.^{2,5,6,15} It is difficult to compare these data with our results because of small number of bacteriological confirmations of the pulmonary infection (8.5%).

Due to the limited accessibility of microbiological tests and the possibility of rapid outcome of the infection in patients with lung cancer the empirical treatment is recommended.¹⁹ Patients with neutropenia below 500/ μ L are conventionally treated with aminoglycoside and β -lactamic antibiotic (amoxicillin + clavulanic acid or cephalosporins of II/III generation). In case of leucopenia above 500/ μ L aminoglycoside and cephalosporin of III generation or cephalosporin of III generation and macrolid are administered. In patients with neutropenia and fever cephalosporin of III generation and clindamycin are applied. In the lack of results of this treatment after 5 days a different etiology must be considered. In case of pneumonia caused by *Pneumocystis carinii* (PCP) trimetoprim-sulfametoxazol is usually applied.^{13,18} In cases of infections caused by fungi patients are treated with amphotericin B.^{2,7,20,21} In the examined group cephalosporins of II/III generation, amoxicillin with clavulanic acid and aminoglycosides were most frequently applied.

Severe pulmonary infections in lung cancer patients may develop due to local or systemic immunological disorders. Systemic immunological disturbances occur relatively early in patients with lung cancer. Irregularities concern mainly the cellular type of immunity.^{6,22} What is advantageous to infections is also permeability disorder of bronchus caused by helophytic or intramural increase of the neoplasm or by the pressure to a bronchus wall caused by the mass of the tumour or enlarged lymph nodes. These phe-

nomena are intensified by the impaired cough reflex which may take place against the background of applied therapy (narcotics, psychotropic) or as a result of neoplastic metastases to brain.²³ Moreover, metastases to bone marrow may lead to leucopenia and anaemia.^{2,6,24} It seems that in our patients the main causes of pneumonia were atelectasis and dysfunction of phagocytes and lymphocytes (with normal or increased WBC), especially in NSCLC.

Another group of factors predisposing to the occurrence of the respiratory system infection includes those connected with the radical and palliative treatment for lung cancer. Most of drugs applied in the antineoplastic therapy have a suppressive effect on the function of the immune system. Alkalisating drugs, antimetabolites of purines, pyrimidines and folic acid produce the stronger immunosuppressive effect.^{22,25} Almost all cytostatics create disorders of proliferation and function of granulocytes with a temporary shortage of these cells in the peripheral blood. In SCLC group of patients 60% received chemotherapy with cisplatin, etoposide or cyclophosphamide, adriablastine and vincristine and all of patients were treated with glucocorticosteroids. The risk of the infection increases considerably in patients whose number of neutrophils does not exceed 500/ μl and is especially high in the case of neutropenia below 100/ μl .^{10,25} Glucocorticoids are often used as supportive drugs in lung cancer patients. By the suppressive influence on the cellular immunity they contribute to the increase of susceptibility to infections.¹²

The syndrome produced by radiotherapy depends on the size of irradiated area and the amount of a total dose. Developing inflammatory changes in lungs may be responsible for the occurrence of respiratory failure and the patients' death, especially with this state being often complicated by the respiratory system infection.^{2,3,26}

It is estimated that over 80% of patients do

not survive the first year since the diagnosis, and only few per cent survive 5 years.^{1,10} Similarly in the examined group the median of the patients' survival was 9 months (NSCLC: 12 months; SCLC: 8 months). Our results indicated additionally that the high intensity of pulmonary inflammation measured by WBC and the extent of radiological changes are connected with a poor prognosis and short period of hospitalisation. This was confirmed by our previous studies. The negative correlation between the serum concentration of lipid hydroperoxides and radiological regression was observed in patients with pneumonia after 14-days therapy.²⁷ Moreover, in patients with tuberculosis, the serum concentration of other inflammatory indicators such as conjugated dienes, thiobarbituric acid-reactive substances,²⁸ soluble tumour necrosis factor receptor I, and intercellular adhesion molecule-1 were significantly higher in the radiologically advanced disease.²⁹

Conclusions

(1) Lung cancer was the main cause of death among our patients; (2) Pneumonia was diagnosed in 58.5% as a secondary cause of death in lung cancer patients; (3) In patients with SCLC, the extent of inflammatory changes on chest X-ray and WBC correlated negatively with the period of hospitalisation.

References

1. Jassem J, Papliński Z. *Lung cancer*. Warszawa: PZWL; 1994.
2. Remiszewski P. Supporting care in lung cancer. *Nowa Klinika* 1999; 6: 324-28.
3. Spiro SG. Lung cancer. *Eur Respir Monogr* 2001; 17: 22-48.
4. Brown BW, Brauner C, Minnotte MC. Noncancer deaths in white adult cancer patients. *J Natl Cancer Inst* 1993; 85: 979-87.

5. Zych J, Szymańska D, Drozd I, Słupek A, Rowińska-Zakrzewska E. Infections as a cause of death in patients with lung cancer. *Pneumonol Pol* 1984; **52**: 11-7.
6. Remiszewski P, Słodkowska J, Wiatr E, Zych J, Załęska J, Radzikowska E, et al. Infections as a main and additional cause of death in patients treated due to small cell lung cancer. *Pneumonol Alergol Pol* 1999; **67**: 347-53.
7. Varthalitis I, Aoun M, Daneau D, Meunier F. *Pneumocystis carinii* Pneumonia in patients with cancer. *Cancer* 1993; **71**: 481-5.
8. Mulder J. *Haemophilus influenzae* as an ubiquitous cause of common acute and chronic purulent bronchitis. *Acta Med Scand* 1938; **43**: 94-8.
9. Lanyi M. Über den begriff des bakteriellen bronchialinfektes. *Dtsch Med Wschr* 1968; **49**: 2390-93.
10. Putinati S, Trevisani L, Gualandi M, Guerra G, Rossi MR, Sartori S, et al. Pulmonary infections in lung cancer patients at diagnosis. *Lung Cancer* 1994; **11**: 243-9.
11. Nagata N, Nikaido Y, Kido M, Ishibashi T, Sueishi K. Terminal pulmonary infections in patients with lung cancer. *Chest* 1993; **103**: 1739-42.
12. Maschmeyer G, Link H, Hiddemann W, Meyer P, Helmerking H, Eisenmann E, et al. Pulmonary Infiltrations in Febrile Patients with Neutropenia. *Cancer* 1994; **73**: 2296-304.
13. Masur H, Shelhamer J, Parrillo JE. The management of pneumonias in immunocompromised patients. *JAMA* 1985; **235**: 1769-73.
14. Tamm M, Traenkle P, Grilli B, Soler M, Bollinger CT, Dalquen P, et al. Pulmonary cytomegalovirus infection in immunocompromised patients. *Chest* 2001; **119**: 838-43.
15. Remiszewski P, Słodkowska J, Wiatr E, Szczepek B, Radomski P, Rowińska-Zakrzewska E. Mycosis and pneumocystis carini pneumonia as a cause of death in patients treated due to small cell lung cancer. *Pneumonol Alergol Pol* 1998; **66 (Suppl 2)**: S173.
16. Kuan-Yu C, Shiann-Chin K, Po-Ren H, Kwen-Tay L, Pan-Chyr Y. Pulmonary fungal infection, emphasis on microbiological spectra, patient outcome and prognostic factors. *Chest* 2001; **120**: 177-84.
17. Kanda Y, Yamamoto R, Chizuka A, Hamaki T, Suguro M, Arai Ch, et al. Prophylactic action of oral fluconazole against fungal infection in neutropenic patients. A meta-analysis of 16 randomized controlled trials. *Cancer* 2000; **89**: 1611-25.
18. Fossieck BE, Spagnolo SV. *Pneumocystis carinii* pneumonitis in patients with lung cancer. *Chest* 1980; **78**: 721-2.
19. Talcott JA, Siegel RD, Finberg R, Goldmann L. Risk assessment in cancer patients with fever and neutropenia: A prospective, two-centre validation of a prediction rule. *J Clin Oncol* 1992; **10**: 316-22.
20. Jarvis WR. Epidemiology of nosocomial fungal infections with emphasis of *Candida* species. *Clin Infect Dis* 1995; **20**: 1526-30.
21. Rubenstein EB, Rolston K, Benjamin RS, Loewy J, Escalante C, Manzullo E, et al. Outpatient treatment of febrile episodes in low-risk neutropenic patients with cancer. *Cancer* 1993; **71**: 3640-6.
22. van Meerten E, Verweij J, Schellens JHM. Antineoplastic agents. Drug interaction of clinical significance. *Drug Staf* 1995; **12**: 168-82.
23. Law A, Karp DD, Dipetrillo T, Daly BT. Emergence of increased cerebral metastasis after high dose preoperative radiotherapy with chemotherapy in patients with locally advanced nonsmall cell lung carcinoma. *Cancer* 2001; **92**: 160-4.
24. Remiszewski P, Słodkowska J, Szczepek B, Zwolska Z, Radomski P, Byszevska D, et al. Etiology of infection as a main and additional cause of death in patients treated due to small cell lung cancer. *Pneumonol Alergol Pol* 1999; **67**: 354-61.
25. Earle CC, Stewart DJ, Cormier Y, Evans WK, Gertler SZ, Mihalicioiu C, et al. A phase I study of gemcitabine/ cisplatin/ etoposid in the treatment of small-cell lung cancer. *Lung Cancer* 1998; **22**: 235-41.
26. Ali MA, Kraut MJ, Valdivieso M, Merskovic AM, Du W, Kalemkerian GP. Phase II study of hiperfractionated radiotherapy and concurrent weekly alternating chemotherapy in limited-stage small cell lung cancer. *Lung Cancer* 1998; **22**: 39-44.
27. Nowak D, Zięba M, Zawiasa D, RoŃniecki J, Król M. Changes of serum concentration of lipid peroxidation products in patients with pneumonia. *Monaldi Arch Chest Dis* 1996; **51**: 188-93.
28. Kwiatkowska S, Piasecka G, Zięba M, Piotrowski W, Nowak D. Increased serum concentration of conjugated dienes and malondialdehyde in patients with pulmonary tuberculosis. *Respir Med* 1999; **93**: 272-6.

29. Kwiatkowska S, Kuźmińska B, Zięba M, Kroczyńska-Bednarek J, Kuna P. Enhanced concentration of circulating ICAM-1 and TNF receptor I in patients with pulmonary tuberculosis. *Current Pneumology* 1999; **3**: 225-30.