

Department of Thoracic Surgery, Medical University of Lublin  
Department of Pharmaceutical Microbiology, Medical University of Lublin

FRANCISZEK FURMANIK, PAWEŁ RYBOJAD, ANNA KASPRZYCKA,  
IZABELA KORONA-GŁOWNIAK, ANNA MALM

*Preoperative chemotherapy as a predisposing factor  
for colonization of upper respiratory tract with Candida spp.  
in patients with non-small cell lung cancer*

Surgery remains the best treatment in non-small cell lung cancer (NSCLC), when a complete resection of the tumor and the mediastinal nodes is possible (5,6). Otherwise, preoperative chemotherapy is included. The purpose of such therapy is to reduce the volume of the tumor and the nodes, and to treat the distant undetectable metastasis in order to improve survival (1,5,6). The type and dose of chemotherapeutics depends on histological type of tumor and its staging in the time of diagnosis. Despite therapeutic influence, chemotherapy can also cause many undesirable side effects. One of them is deficiency in the immune system, which can be regarded as a risk factor of colonization of upper respiratory tract with some pathogenic or opportunistic microorganisms (11). Resident or transient members of microflora of nasopharynx are a potential reservoir for endogenous respiratory tract infections, which are an important medical problem among patients with lung cancer (7,13). Several of these microorganisms are described as pathogens in immunocompromised patients, especially during oral mucositis as a result of high-dose chemotherapy, profound and prolonged neutropenia, increasing use of long-dwelling intravascular catheters (15).

The aim of the present paper was to assay the composition of nasopharyngeal microflora in patients with NSCLC without or with preoperative chemotherapy.

#### MATERIAL AND METHODS

**Patient population.** 48 patients with NSCLC (carcinoma planoepithelialae, adenocarcinoma, carcinoma macrocellulare) aged 37–73 years (46 men and 4 women, mean age of 61.5 years) were included in the present study. They were divided into two groups: (I) 20 patients from control group (17 men and 3 women with the mean age of 60.3 years) and (II) 28 patients who received at least one course of preoperative chemotherapy (27 men and 1 woman with the mean age of 62.7 years). None of the patients had any clinical (normal body temperature) or laboratory signs of infections (normal leukocyte count).

**Microbiological assay.** Throat and nasal specimens were taken from each patient on the day of hospital admission (in group II the patients were already after at least one course of

chemotherapy). The routine microbiological methods were used for isolation and identification of microorganisms (4).

Statistical analysis. Correlation between preoperative chemotherapy and colonization of upper respiratory tract by pathogenic or opportunistic microflora was also assessed on the basis of estimation of relative risk (RR) and 95% confidence interval (CI) (10).

## RESULTS

The increased prevalence of pathogenic or opportunistic microflora was observed in throat specimens in patients with NSCLC after preoperative chemotherapy (Tab. 1). In contrast, the frequency of occurrence of such microflora in nasal specimens were comparable in both studied groups (Tab. 1). A detailed analysis of the isolated species from throat or nasal specimens indicate that there were no significant differences in the frequency of occurrence of *Staphylococcus aureus* and Gram-negative rods in patients of both groups (Tab. 2). The frequ-

Table 1. The frequency of occurrence of pathogenic or opportunistic microflora in throat or nasal specimens from patients with NSCLC

Group of patients	Number (percent) of patients			
	Pathogenic or opportunistic microflora*		Normal microflora	
	Throat	Nose	Throat	Nose
Control (n = 20)	4 (20.0%)	5 (25.0%)	16 (80.0%)	15 (75.0%)
"Chemotherapy" (n = 28)	8 (28.6%)	7 (25.0%)	20 (71.4%)	21 (75.0%)

\* In 1 patient from control group and in 4 patients of "chemotherapy" group pathogenic species were isolated from both throat and nasal specimens

Table 2. The frequency of occurrence of some pathogenic or opportunistic species in throat or nasal specimens in patients with NSCLS

Group of patients	Pathogenic or opportunistic species*	Number (percent) of patients		
		Throat	Nose	
Control (n = 20)	<i>Candida albicans</i>	2 (10.0%)	-	
	<i>Staphylococcus aureus**</i>	2 (10.0%)	4 (20.0%)	
	Gram-negative rods	<i>Pseudomonas stutzeri</i>	-	1 (5.0%)
		<i>Klebsiella pneumoniae</i>	1 (5.0%)	-
"Chemiotherapy" (n = 28)	<i>Candida</i> spp.	<i>Candida albicans</i>	7 (25.0%)	
		<i>Candida parapsilosis</i>	1 (3.6%)	
	<i>Staphylococcus aureus</i>		1 (3.6%)	6 (21.4%)
	Gram-negative rods	<i>Pseudomonas aeruginosa</i>	1 (3.6%)	-
		<i>Citrobacter</i> spp.	1 (3.6%)	-
		<i>Serratia</i> spp.	1 (3.6%)	-

\* Two pathogenic species were isolated from throat specimens in 1 patient of control and of "chemotherapy" groups, and from nasal specimens in 2 patients of "chemotherapy" group

\*\* One of the isolated species was identified as methicillin-resistant *S. aureus*

ency of isolation of *Candida* spp. from throat specimens was higher in patients after preoperative chemotherapy compared to that in the control group (Tab. 2). Among yeast-like fungi, *C. albicans* was isolated most frequently; only one isolate was identified as *C. parapsilosis* (Tab. 2). The RR value  $>1$  suggests that preoperative chemotherapy may induce throat colonization by *Candida* spp. (Tab. 3), being without effect on colonization of throat or nose by *S. aureus* or Gram-negative rods - RR values  $< 1$  (data not shown). In none of the patients was *Candida* spp. isolated from nasal specimens (Tab. 2).

Table 3. Correlation between preoperative chemotherapy and colonization of throat by pathogenic or opportunistic microflora, including *Candida* spp. in patients with NSCLS

Unfavourable state	Relative risk (RR)	95% confidence interval (CI)
Colonization of throat by pathogenic or opportunistic microflora	1.43	0.43-4.75
Colonization of throat by <i>Candida</i> spp.	2.86	0.61-13.47

## DISCUSSION

The clinical course of lung cancer is frequently complicated by respiratory tract infections, mainly pulmonary infections (13). Generally, such infections secondary to lung cancer occur due to defects in the clearance system in sites peripheral to the bronchial obstruction or stenosis (13). Some reports indicate that patients with lung cancer are significantly more frequently colonized by bacteria in the upper respiratory tract (7) compared to healthy people (8). In these patients, several treatments such as chemotherapy, radiotherapy or administration of immunosuppressive agents, e.g. steroids may further depress their immunological state in addition to the underlying disease itself (7).

It is well-known that chemotherapy-induced neutropenia may favour nasopharyngeal colonization by some opportunistic microorganisms (11). However, only short-term, transient myelosupresion was observed in lung cancer patients after chemotherapy (11). This is in accordance with our data indicating that the prevalence of *S. aureus* and Gram-negative rods in the upper respiratory tract in patients with NSCLC both in the control group and that treated with preoperative chemotherapy is relatively low and comparable to that in general population (4). The studies observed that frequency of throat colonization by *Candida* spp. in patients with NSCLC from control group is also relatively low but increased significantly after preoperative chemotherapy. Our data suggest that this treatment can be regarded as a predisposing factor for prevalence of *Candida* spp. in the throat in patients with NSCLC. In consequence, such colonization may be a precursor to candidiasis of respiratory tract or/and candidemia (3, 14). According to the literature (12), the risk for nosocomial infection is as high as 38% with colonization by *Candida* spp. in critically ill surgical patients. *C. albicans* is still a major opportunistic human pathogen (2) but other species, e.g. *C. parapsilosis* have been increasingly reported as pathogens (9). Moreover, non-albicans *Candida* species are inherently or secondarily resistant to some antifungal drugs, e.g. fluconazole, implying therapeutic problems (9).

Our preliminary results emphasize a need to perform microbiological screening of the upper respiratory tract in patients with lung cancer in order to assess the actual risk of respiratory infections in a given population in the light of known local variability with respect to species distribution.

## CONCLUSIONS

1. The prevalence of *S. aureus* and Gram-negative rods on the mucous membranes of throat and/or nose in patients with NSCLC both in control group and that treated with preoperative chemotherapy was comparable and relatively low.

2. The frequency of colonization of throat mucous membranes by *Candida* spp. in patients with NSCLC was also relatively low but increased significantly after preoperative chemotherapy, which suggests that this treatment can be regarded as a predisposing factor for such an unfavourable state.

## REFERENCES

1. Bass P.: Inductive and adjuvant treatment strategies for localized nonsmall cell lung cancer. *Curr. Opin. Oncol.*, 14, 180, 2002.
2. Calderone R. A., Fonzi W. A.: Virulence factors of *Candida albicans*. *Trends Microbiol.*, 9, 327, 2001.
3. Batura-Gabryel H. et al.: Ocena występowania zakażenia grzybiczego u chorych z rakiem płuca. *Mikol. Lek.*, 1, 101, 1994.
4. Campos J.M. et al.: Specimen collection and processing. [In:] *Clinical and Pathogenic Microbiology*. Eds. B. J. Howard, J.F. Keiser, T. F. Smith, A. S. Weissfeld, R. C. Tilton, Mosby, 213, St. Louis, 1994.
5. Doddoli C. et al.: Postoperative complications in relation with induction therapy for lung cancer. *Eur. J. Cardio-thoracic Surg.*, 20, 385, 2001.
6. Furmanik et al.: Odległe wyniki leczenia skojarzonego z udziałem przedoperacyjnej chemioterapii i resekcji u chorych na miejscowo zaawansowanego niedrobnokomórkowego raka płuca. *Pneumonol. Alergol. Pol.*, 70, 34, 2002.
7. Hirakata Y. et al.: Bacterial colonization of the upper respiratory tract of patients with primary lung cancer and nonmalignant lung disease. *Chemotherapy*, 43, 400, 1997.
8. Howard B. J., Rees J.C.: Host-parasite interactions: mechanisms of pathogenicity. [In:] *Clinical and Pathogenic Microbiology*. Eds. B.J. Howard, J.F. Keiser, T.F. Smith, A.S. Weissfeld, R.C. Tilton, Mosby, 9, St. Louis 1994.
9. Kremery V., Barnes A.J.: Non-albicans *Candida* spp. causing fungemia: pathogenicity and antifungal resistance. *J. Hosp. Infect.*, 50, 243, 2002.
10. Landry M.D., Sibbald W. J.: From data to evidence: evaluative methods in evidence-based medicine. *Respir. Care*, 46, 1226, 2001.
11. Minah G.E. et al.: Oral succession of Gram-negative bacilli in myelosuppressed cancer patients. *J. Clin. Microbiol.*, 24, 210, 1986.
12. Pittet D. et al.: *Candida* colonization and subsequent infections in critically ill surgical patients. *Ann. Surg.*, 220, 751, 1994.
13. Putinati S. et al.: Pulmonary infections in lung cancer patients at diagnosis. *Lung Cancer*, 11, 243, 1994.
14. Safdar N., Maki D.G.: The commonality of risk factors for nosocomial colonization and infection with antimicrobial resistant *Staphylococcus aureus*, *Enterococcus*, Gram-negative bacilli, *Clostridium difficile*, and *Candida*. *Ann. Intern. Med.*, 136, 834, 2002.
15. Zinner S.H.: Changing epidemiology of infections in patients with neutropenia and cancer: emphasis on gram-positive and resistant bacteria. *Clin. Infect. Dis.*, 29, 490, 2000.

## SUMMARY

In the present study 48 patients with non-small cell lung cancer (NSCLC) were included – 20 patients from control group and 28 patients after at least one course of preoperative chemotherapy. The analysis of nasopharyngeal microflora in these patients suggests that preoperative chemotherapy can be regarded as a predisposing factor for colonization of mucous membrane of throat with yeast-like fungi – *Candida* spp.

Przedoperacyjna chemioterapia jako czynnik ryzyka sprzyjający kolonizacji górnych dróg oddechowych przez *Candida* spp. u pacjentów z niedrobnokomórkowym rakiem płuca

Badaniami objęto 48 pacjentów z niedrobnokomórkowym rakiem płuca – 20 pacjentów z grupy kontrolnej oraz 28 po co najmniej jednym kursie chemioterapii. Analiza mikroflory nosogardzieli u tych pacjentów sugeruje, że przedoperacyjna chemioterapia może być czynnikiem ryzyka, sprzyjającym kolonizacji błony śluzowej gardła przez grzyby drożdżopodobne z rodzaju *Candida*.