Clinical Characteristics of 45 Patients With Invasive Pulmonary Aspergillosis

Retrospective Analysis of 1711 Lung Cancer Cases

Xi Yan, MD; Mei Li, MD; Ming Jiang, MD; Li-qun Zou, MD; Feng Luo, MD; and Yu Jiang, MD

BACKGROUND: Invasive aspergillosis (IA) is a common complication in patients with hematologic malignancies. Patients with solid tumors also are at risk for IA because they may develop neutropenia as a result of chemotherapy and radiotherapy. However, studies of IA in patients with solid tumors are rare. In this study, the risk factors and clinical characteristics of pulmonary infection and death mediated by invasive pulmonary aspergillosis (IPA) as complications in patients with lung cancer were determined. **METHODS:** The authors conducted a retrospective analysis of the clinical notes from 45 patients who had IPA. **RESULTS:** Among 1711 patients with lung cancer, 45 patients contracted pulmonary aspergillosis (2.63%). There were 10 cases of proven disease and 35 cases of probable disease. In univariate analysis, the main predisposing factors were clinical stage IV disease ($P = .018$), chemotherapy during the month preceding infection ($P = .033$), and corticosteroid use ($\geq$3 days; $P = .038$). In multivariate analysis, only clinical stage IV disease ($P = .018$) was associated with IPA. Furthermore, the mortality rate among lung cancer patients who had pulmonary aspergillosis was 51.1% (23 of 45 patients). Of the patients who died, corticosteroid therapy ($P = .001$) and grade 3/4 neutropenia ($P = .013$) were correlated statistically with pulmonary aspergillosis in patients with lung cancer. **CONCLUSIONS:** In univariate analysis, the risk factors for IPA in lung cancer included chemotherapy and corticosteroid use in the month preceding infection and clinical stage IV disease. However, in multivariate analysis, only clinical stage IV disease was identified as a risk factor for IPA. **Cancer 2009;115:5018–25. © 2009 American Cancer Society.**

KEY WORDS: lung cancer, invasive pulmonary aspergillosis, clinical stage, corticosteroid, neutropenia.

Invasive aspergillosis (IA) is a common complication in severely immunocompromised patients, such as bone marrow transplantation recipients or patients who have received extensive chemotherapy for hematologic malignancies.[1,2] Predisposing factors of IA include neutropenia, chemotherapy, and corticosteroid therapy.[3] Patients with solid tumors also are at risk for IA because they may develop neutropenia as a result of chemotherapy and radiotherapy. However, studies of IA in patients with solid tumors are rare.

Aspergillus is a filamentous fungus found commonly in water, in soil, and especially in decomposing plants. Similar to other fungi, *Aspergillus* spores can be inhaled into the lungs and may cause invasive pulmonary

Corresponding author: Yu Jiang, MD, Department of Medical Oncology of Cancer Center, State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu 610041, People's Republic of China; Fax: (011) 86-28-85423278; jiangyu1973@hotmail.com

Department of Medical Oncology of Cancer Center, State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu, People's Republic of China

The first 2 authors contributed equally to this work.

We thank Chang Liu, MD, for his help during revision.

Received: October 31, 2008; **Revised:** April 7, 2009; **Accepted:** April 8, 2009

Published online July 27, 2009 in Wiley InterScience (www.interscience.wiley.com)

DOI: 10.1002/cncr.24559, www.interscience.wiley.com

aspergillosis (IPA) in certain conditions.[4] Extensive studies have been performed with respect to risk factors for *Aspergillus* infection in patients with chronic lung disease.[5-7] Lung cancer patients commonly have chronic lung diseases; these patients also are predisposed to IPA because of tumor infiltration into the pulmonary tissue as well as neutropenia resulting from chemotherapy or radiotherapy. However, to date, only case reports describing *Aspergillus* infection as a complication of lung cancer have been reported. In addition, 2 other articles have reported methods for the detection of pulmonary aspergillosis in patients with lung cancer, including serologic methods and bronchioalveolar lavage (BAL)-polymerase chain reaction (PCR).[8,9] To the best of our knowledge, excluding the case reports, an analysis of the clinical characteristics of IPA in patients with lung cancer has yet to be performed. To understand the risks and clinical characteristics of IPA in patients with lung cancer, we retrospectively studied all lung cancer inpatients in West China Hospital within the past 8 years, including patients who had lung cancer with proven and probable IPA.

MATERIALS AND METHODS

Patients

From January 1, 2000 to December 31, 2007, all inpatients with lung cancer who were seen in West China Hospital, including those who had IPA as a discharge diagnosis, were analyzed. Inclusion in this analysis required patients who had either proven or probable IPA based on the Revised Definitions of Invasive Fungal Disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group.[10] Proven IPA required histopathologic or microbiologic documentation of infection from tissues obtained by biopsy or in culture samples from a normally sterile site. Probable disease required 1) a host factors, including a recent history of neutropenia, corticosteroids use, or treatment with T-cell immunosuppressants; and 2) clinical features, including the presence of a new infiltrate on a chest computed tomography (CT) scan, such as dense lesions, air crescent signs, or a cavity; and 3) mycologic evidence.

Methods and Definition

A retrospective analysis of chart information on patients with lung cancer was undertaken. If the patient had been admitted on several occasions, then statistical analysis was performed using the data pertaining to their last admission as well as data concerning the patient's overall disease progression. For the patients who did not have aspergillosis infection detected, the "time of IPA diagnosis" was set as their last discharge date. Neutropenia was evaluated and graded according to the National Cancer Institute Common Toxicity Criteria (version 2.0, 1999). Corticosteroid therapy was defined as any amount of corticosteroid (usually the equivalent of doses >66.7 mg daily of prednisone in this study) given as maintenance therapy, pulses, and tapers.[11] Whether a patient died with active IPA was determined according to the medical record as noted by the clinicians who cared for the patients. If a patient died with active IPA, then the patient's cause of death was classified as IPA.[11]

Statistical Analysis

Frequencies and percentages were used for statistical descriptions, and the chi-square test or the Fisher exact test was used for statistical analysis of categorized data within a 4-fold table. Multiple logistic regression analysis was used to estimate the risk factors for IPA. For quantitative data, *t* tests were used. All statistical analyses were carried out using SPSS 13.0 statistical software, and statistical significance was defined as a P value $<.05$.

RESULTS

Rate of Invasive Pulmonary Aspergillosis Infection

From the beginning of January 2000 to the end of December 2007, 1711 patients with lung cancer were treated, resulting in 3071 discharges. Forty-five cases of confirmed IPA infection were detected (2.63%), and the infection rate per discharge was 1.47%. Of the 45 patients who had IPA, the diagnosis was probable in 35 patients and proven 10 patients. Of those with IPA infections, the average patient age was 61 years (range, 40-76 years). Patient characteristics are listed in Table 1.

Table 1. Characteristics of 45 Cases of Invasive Pulmonary Aspergillosis in Patients With Lung Cancer

Characteristics	No. of Patients, n=45	%
Sex		
Men	36	80
Women	9	20
Age, y		
≥60	24	53
<60	21	47
Pathologic type		
SCLC	9	20
NSCLC	36	80
Adenocarcinoma	14	31.1
Squamous cell carcinoma	15	33.3
Others	7	15.6
Clinical stage		
I	3	6.7
II	1	2.2
III	9	20
IV	32	71.1
Complicated with other diseases		
COPD	13	28.9
Chronic hepatitis B	3	6.67
Type II diabetes	2	4.44
Coronary heart disease	2	4.44
Hypertension	5	11.1
Chemotherapy*	20	44.4
Thoracic radiotherapy†	18	40
Neutropenia*‡		
Grade 1-2	5	11.1
Grade 3-4	14	31.1
Corticosteroid therapy*§		
≥3 d	28	62.2
<3 d	3	6.7
Concomitant infection		
Bacterial	7	15.6
Other fungal	11	24.4
Bacterial and other fungal	9	20
Antifungal use for ≥3 d*		
Fluconazole	9	20
Other antifungal agents	0	0
Time of hospitalization†		
≥2 wk	35	77.8
<2 wk	10	22.2
Other treatments used for ≥3 d*		
Deep vein tube indwelling	21	46.7
Transfusion	8	17.8
Thoracic close drainage	10	22.2
Death	23	51.1

SCLC indicates small cell lung cancer; NSCLC, nonsmall cell lung cancer; COPD, chronic obstructive pulmonary disease.
* During the month preceding infection.
† Any time before a diagnosis of invasive pulmonary aspergillosis.
‡ According to the National Cancer Institute Common Toxicity Criteria (version 2.0, 1999).
§ Corticosteroid therapy included any amount of corticosteroid given as maintenance therapy, pulses, and tapers.

Table 2. Univariate Analysis of Risk Factors for Invasive Pulmonary Aspergillosis in 1711 Patients with Lung Cancer

Characteristics	No. of Patients With Lung Cancer, N=1711	No. of Patients With Infection, n=45	Infection Rate, %	*P*
Sex				.247
Men	1235	36	2.91	
Women	476	9	1.89	
Age, y				.462
≥60	820	24	2.93	
<60	891	21	2.36	
Pathologic type				.473
NSCLC	1437	36	2.51	
SCLC	274	9	3.28	
Clinical stage				.018
I-III	799	13	1.63	
IV	912	32	3.51	
Chemotherapy*				.033
Yes	508	20	3.94	
No	1203	25	2.08	
Thoracic radiotherapy†				.587
Yes	754	18	2.39	
No	957	27	2.82	
Corticosteroid therapy ≥3 d*‡				.038
Yes	797	28	3.51	
No	914	17	1.86	

SCLC indicates small cell lung cancer; NSCLC, nonsmall cell lung cancer.
* During the month preceding infection.
† Anytime before a diagnosis of invasive pulmonary aspergillosis.
‡ Corticosteroid therapy included any amount of corticosteroid given as maintenance therapy, pulses, and tapers.

Risk Factors for Invasive Pulmonary Aspergillosis in Patients With Lung Cancer

Table 2 indicates that, in univariate analysis, the main predisposing factors were clinical disease stage (stage IV), chemotherapy during the month before infection, and corticosteroid use. However, in multivariate analysis, only clinical stage IV disease (odds ratio, 2.199; 95% confidence interval, 1.146-4.219; $P = .018$) was associated with IPA.

Relation Between Invasive Pulmonary Aspergillosis and Time of Year

Figure 1a shows that there was no statistically significant relation detected between the month of IPA infection (January to December) among the 45 patients with lung cancer (chi-square statistic, 16.2; $P = .134$). In addition, a 3-month moving average was calculated, no statistically significant relation was observed (Fig. 1b) (chi-square statistic, 6.467; $P = .091$).

Prognosis

Of the 45 patients with lung cancer who had IPA infections, 51.1% (23 of 45 patients) died as a result of IPA infection (Table 1). Among those 23 patients, 17 (73.9%) died within 1 month of their IPA diagnosis. The prognostic factors for patients with IPA are listed in Table 3.

DISCUSSION

Patients with hematologic malignancies and those undergoing hematopoietic stem cell transplantation are at high risk for IA infection.[1,2,10] The infection rate is between 1.1%-15.1%.[1,12-14] IA infection rates for patients with solid tumors are relatively lower but can be common in patients with neutropenia.[15] Previous studies revealed that the IA infection rate for patients with solid tumors is nearly 0.70%.[16,17] However, data from the current study revealed the lung cancer IPA infection rate was 2.63%, which was comparatively higher than the rates reported in the 2 previous studies. Several factors may account for this

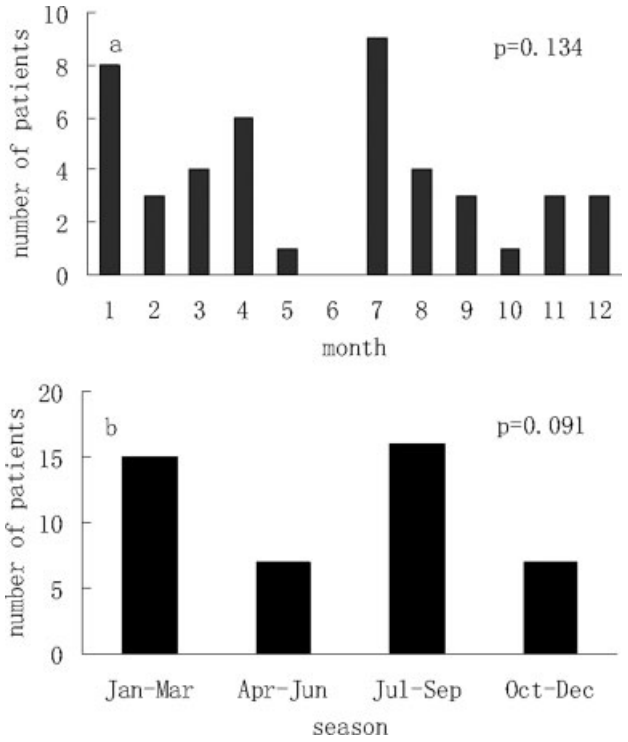

FIGURE 1. These charts illustrate the relation between invasive pulmonary aspergillosis (IPA) and season. (a) There was no statistically significant correlation detected between the month of IPA infection (January to December). (b) When a 3-month moving average was calculated, no statistically significant correlation was observed.

Table 3. Risk Factors for Overall Mortality in 45 Cases of Invasive Pulmonary Aspergillosis Among Patients With Lung Cancer

Characteristics	No. of Patients (%) Survival, n=22	Death, n=23	*P*
Women	6 (27)	3 (13)	.284*
Median age [range], y	57 [40-74]	66 [45-76]	.083
Corticosteroid therapy†	10 (45)	21 (91)	.001
Antifungal therapy			
Before diagnosis (fluconazole)	1 (4.5)	8 (34.8)	.022*
After diagnosis (itraconazole)	22 (100)	20 (87)	.233*
Proven infection	4 (18)	6 (26)	.722*
Concomitant infection	12 (55)	15 (65)	.465
Clinical stage IV disease	13 (59)	19 (83)	.082
Grade 3-4 neutropenia‡	3 (14)	11 (48)	.013

* Fisher exact probability.
† Corticosteroid therapy included any amount of corticosteroid given as maintenance therapy, pulses, and tapers.
‡ According to National Cancer Institute Common Toxicity Criteria (version 2.0, 1999).

finding. First, in the previous studies, the IA infections were diagnosed based on autopsy; however, the mortality rate among patients with IPA in our study was only 51.1% (Table 1). Second, all patients in the current study had lung cancer, and the majority of lung cancer patients have other pulmonary comorbidities and immunodeficiency.[7,18,19] Thus, these patients will be most likely to develop IPA infection compared with patients who have other solid tumors.

Other studies revealed much high aspergillosis infection rates in patients with lung cancer (range, 14.2%-40.6%).[8,9] Possible reasons for this discrepancy include: 1) Not all patients with lung cancer in the current study underwent investigations for aspergillosis infection; therefore, some infected patients may have been missed, because the symptoms of aspergillosis infection may have been masked by the symptoms of lung cancer and may have gone unnoticed. 2) All of the patients who were selected for the studies by Shahid et al underwent bronchoscopy as well as BAL. Unless there are special circumstances, most patients who have proven metastatic lung cancer and those who undergo surgery do not need to undergo these 2 procedures. Therefore, it is likely that the sample of patients selected in the previous reports had a pulmonary fungal infection to begin with.

Risk factors of IA infection in patients with hematologic malignancy and those undergoing hematopoietic stem cell transplantation have been well documented. These risk factors include neutropenia, corticosteroid treatment, immunosuppressive therapy, chemotherapy, pulmonary disease, decreased pulmonary function, etc.[3,20-25] Data from the current study confirmed that chemotherapy, corticosteroid therapy, and clinical stage were among the risk factors for IPA infection in univariate analysis (Table 2). These factors coincided with the risk factors of pulmonary fungal infection (including aspergillosis) in the patients with solid tumor reported previously.[26] However, in multivariate analysis, only clinical stage IV disease was associated with IPA. These patients often are similar to patients with advanced disease and have increased complications and decreased immunity. Another study also reported that pulmonary fungal infection was associated with clinical stage in patients with lung cancer.[27]

Because the fungal load in the air may be relatively lower in winter, pulmonary aspergillosis is more common in the summer/autumn seasons because of increased humidity and high environmental fungal load.[28] Wald et al[29] revealed that season, namely summer, is a risk factor for IA infection in allogeneic hematopoietic stem cell transplantation recipients. Jiang et al[26] reported that peak fungal infections, such as Moniliasis in patients with solid tumors, occur during September and October. However, numerous studies also have revealed that air fungal load and season are independent of IA infection.[1,30] Data from the current study confirmed that season is independent of IA infection (Fig. 1). Nevertheless, because of the small sample size, the relation between lung cancer IPA infection, season, and air fungal load requires further research with greater sample sizes.

The mortality rate for patients with lung cancer who had IPA was 51.1% (Table 1). A previous study reported a mortality rate of approximately 60% in patients with IA.[21] Furthermore, the mortality rate of those undergoing bone marrow transplantation was about 90%.[21]

In determining factors for predicting the prognosis of patients with IA infections, it has been demonstrated that neutropenia and corticosteroid therapy can hasten patient death.[3,31-33] Patients with lung cancer are more susceptible to nosogenic microorganism growth because of changes in the respiratory tract structure, and infiltration of tumors into the bone marrow and radiotherapy often can induce neutropenia in these patients. Variables like chemotherapy preparation, chemotherapy antiemetics, and elevated intracranial pressure from brain metastases normally require corticosteroid treatment; however, the treatment (corticosteroid) not only can increase the rate of fungal growth but also can change the phagocytic function of megalophages, neutrophils, and monocytes against fungal spores and mycelium.[34] Data from the current study revealed that the prognosis for patients who had lung cancer and IPA infection was related to grade 3/4 neutropenia and corticosteroid therapy (Table 3).

Although many articles have reported that early antifungal therapy can improve prognosis,[24,25,31,33,35-37] some have suggested otherwise.[11] Data from the current study revealed that prior prophylaxis with fluconazole, which is devoid of anti-*Aspergillus* activity, could not improve survival. In addition, data from this retrospective study failed to confirm that itraconazole (used when IPA was diagnosed) could improve patient outcomes (Table 3). Recently, with the discovery of new antifungal medications, better outcomes for patients with IPA have been observed. These mold-active antifungal agents include voriconazole,[36] amphotericin B,[37] caspofungin,[35] etc.

The following are limitations of this study: 1) The single-institutional, retrospective nature of this study is a limitation. Because of incomplete medical records, some "potential risk factors" could not be examined. These factors include the time from lung cancer diagnosis, the number of lines of prior chemotherapy, and the recurrence of original disease, which has been reported as a risk factor for invasive fungal infection in pediatric patients with hematologic malignancies.[38] However, very few studies of IA in patients with solid tumors exist. To the best of our knowledge, there has not been a systemic study regarding lung cancer patients with IPA. 2) Lung cancer outpatients were ignored in this study. Data on these patients should be considered in future studies, especially prospective studies. 3) A proven diagnosis of IPA was rare and represented only 22.2% of the patients we analyzed, whereas the majority of patients had a probable diagnosis of IPA. However, the early diagnosis of IPA is challenging,[8,39] especially because patients with lung cancer have baseline disease that covers the signs and symptoms of IPA infection, making a proven diagnosis difficult. Fiberoptic bronchoscopy and percutaneous puncture lung biopsies have potential risks for weak patients,[40] and some patients with advanced-stage lung cancer cannot lay supine for a CT examination. Therefore, for these patients, noninvasive or minimally invasive investigations, such as hematologic tests and PCR tests, should be considered.[8,9,41] 4) Patients with lung cancer may be more prone to *Aspergillus* colonization on the basis of abnormal airways, anatomy, and long-term smoking. A positive BAL fluid culture also may be a "false-positive" result (colonization), similar to the issue in lung transplantation recipients.[42] A positive BAL culture as the microbiologic criteria may not have the same predictive value in this patients population that it has in patients with hematologic malignancies. Actually, the EORTC/MSG group concluded that, currently, the body of evidence supporting a diagnosis of "probable IPA" is not sufficiently mature.[10]

In summary, the main predisposing factors of IPA were clinical stage IV disease, chemotherapy during the

month preceding infection, and corticosteroid use in univariate analysis. However, in multivariate analysis, only clinical stage IV disease was associated with IPA. Risk factors for death in patients with lung cancer who have IPA are corticosteroid therapy and grade 3/4 neutropenia. Therefore, reasonable use of corticosteroids and the prevention or active treatment of grade 3/4 neutropenia are necessary for lowering the incidence and mortality rates for patients with lung cancer who have IPA.

Conflict of Interest Disclosures

The authors made no disclosures.

References

1. Cornet M, Fleury L, Maslo C, Bernard JF, Brucker G; Invasive Aspergillosis Surveillance Network of the Assistance Publique-Hopitaux de Paris. Epidemiology of invasive aspergillosis in France: a 6-year multicentric survey in the Greater Paris area. *J Hosp Infect*. 2002;51:288-296.
2. Herbrecht R, Moghaddam A, Mahmal L, Natarajan-Ame S, Fornecker LM, Letscher-Bru V. Invasive aspergillosis in the hematologic and immunologic patient: new findings and key questions in leukemia. *Med Mycol*. 2005;43(suppl 1):S239-S242.
3. Kiertiburanakul S, Thibbadee C, Santanirand P. Invasive aspergillosis in a tertiary-care hospital in Thailand. *J Med Assoc Thai*. 2007;90:895-902.
4. Soubani AO, Chandrasekar PH. The clinical spectrum of pulmonary aspergillosis. *Chest*. 2002;121:1988-1999.
5. Shahid M, Malik A, Bhargava R. Prevalence of aspergillosis in chronic lung diseases. *Indian J Med Microbiol*. 2001;19: 201-205.
6. Denning DW. Invasive aspergillosis. *Clin Infect Dis*. 1998; 26:781-803.
7. Park CK, Jheon S. Results of surgical treatment for pulmonary aspergilloma. *Eur J Cardiothorac Surg*. 2002;21:918-923.
8. Shahid M, Malik A, Bhargava R. Bronchogenic carcinoma and secondary aspergillosis—common yet unexplored: evaluation of the role of bronchoalveolar lavage-polymerase chain reaction and some nonvalidated serologic methods to establish early diagnosis. *Cancer*. 2008;113:547-558.
9. Malik A, Shahid M, Bhargava R. Prevalence of aspergillosis in bronchogenic carcinoma. *Indian J Pathol Microbiol*. 2003;46:507-510.
10. De Pauw B, Walsh TJ, Donnelly JP, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis*. 2008;46:1813-1821.
11. Burgos A, Zaoutis TE, Dvorak CC, et al. Pediatric invasive aspergillosis: a multicenter retrospective analysis of 139 contemporary cases. *Pediatrics*. 2008;121:e1286-e1294.
12. Ninin E, Milpied N, Moreau P, et al. Longitudinal study of bacterial, viral, and fungal infections in adult recipients of bone marrow transplants. *Clin Infect Dis*. 2001;33: 41-47.
13. Marr KA, Carter RA, Boeckh M, Martin P, Corey L. Invasive aspergillosis in allogeneic stem cell transplant recipients: changes in epidemiology and risk factors. *Blood*. 2002;100: 4358-4366.
14. Grow WB, Moreb JS, Roque D, et al. Late onset of invasive *Aspergillus* infection in bone marrow transplant patients at a university hospital. *Bone Marrow Transplant*. 2002;29: 15-19.
15. Subira M, Martino R, Franquet T, et al. Invasive pulmonary aspergillosis in patients with hematologic malignancies: survival and prognostic factors. *Haematologica*. 2002;87: 528-534.
16. Ohmagari N, Raad II, Hachem R, Kontoyiannis DP. Invasive aspergillosis in patients with solid tumors. *Cancer*. 2004;101:2300-2302.
17. Groll AH, Shah PM, Mentzel C, Schneider M, Just-Nuebling G, Huebner K. Trends in the postmortem epidemiology of invasive fungal infections at a university hospital. *J Infect*. 1996;33:23-32.
18. Caras I, Grigorescu A, Stavaru C, et al. Evidence for immune defects in breast and lung cancer patients. *Cancer Immunol Immunother*. 2004;53:1146-1152.
19. Gao Y, Tang W, Dai X, et al. Effects of water-soluble *Ganoderma lucidum* polysaccharides on the immune functions of patients with advanced lung cancer. *J Med Food*. 2005;8:159-168.
20. Patterson TF, Kirkpatrick WR, White M, et al. Invasive aspergillosis. Disease spectrum, treatment practices, and outcomes. I3 Aspergillus Study Group. *Med (Baltimore)*. 2000;79:250-260.
21. Lin SJ, Schranz J, Teutsch SM. Aspergillosis case-fatality rate: systematic review of the literature. *Clin Infect Dis*. 2001;32:358-366.
22. Crassard N, Hadden H, Pondarre C, et al. Invasive aspergillosis and allogeneic hematopoietic stem cell transplantation in children: a 15-year experience. *Transpl Infect Dis*. 2008;10:177-183.
23. Soubani AO, Qureshi MA. Invasive pulmonary aspergillosis following bone marrow transplantation: risk factors and diagnostic aspect. *Haematologia (Budap)*. 2002;32:427-437.
24. Nosari A, Oreste P, Cairoli R, et al. Invasive aspergillosis in haematological malignancies: clinical findings and management for intensive chemotherapy completion. *Am J Hematol*. 2001;68:231-236.
25. Reichenberger F, Habicht JM, Gratwohl A, Tamm M. Diagnosis and treatment of invasive pulmonary aspergillosis in neutropenic patients. *Eur Respir J*. 2002;19:743-755.

26. Jiang Y, Li JY, Li M, Zhou L, Peng F, Wei YQ. Clinical analysis of nosocomial pulmonary fungal infection in patients with cancer. *Ai Zheng*. 2004;23:1707-1709.
27. Batura-Gabryel H, Firlik M, Wieczorek U. Evaluation of occurrence of fungal infection in patients with lung cancer. *Med Dosw Mikrobiol*. 1994;46:79-81.
28. Panagopoulou P, Filioti J, Petrikkos G, et al. Environmental surveillance of filamentous fungi in 3 tertiary care hospitals in Greece. *J Hosp Infect*. 2002;52:185-191.
29. Wald A, Leisenring W, van Burik JA, Bowden RA. Epidemiology of *Aspergillus* infections in a large cohort of patients undergoing bone marrow transplantation. *J Infect Dis*. 1997;175:1459-1466.
30. Hospenthal DR, Kwon-Chung KJ, Bennett JE. Concentrations of airborne *Aspergillus* compared to the incidence of invasive aspergillosis: lack of correlation. *Med Mycol*. 1998; 36:165-168.
31. Upton A, Kirby KA, Carpenter P, Boeckh M, Marr KA. Invasive aspergillosis following hematopoietic cell transplantation: outcomes and prognostic factors associated with mortality. *Clin Infect Dis*. 2007;44:531-540.
32. Guiot HF, Fibbe WE, van 't Wout JW. Risk factors for fungal infection in patients with malignant hematologic disorders: implications for empirical therapy and prophylaxis. *Clin Infect Dis*. 1994;18:525-532.
33. Caillot D, Casasnovas O, Bernard A, et al. Improved management of invasive pulmonary aspergillosis in neutropenic patients using early thoracic computed tomographic scan and surgery. *J Clin Oncol*. 1997;15:139-147.
34. Berenguer J, Allende MC, Lee JW, et al. Pathogenesis of pulmonary aspergillosis. Granulocytopenia versus cyclosporine and methylprednisolone–induced immunosuppression. *Am J Respir Crit Care Med*. 1995;152:1079-1086.
35. Li D, Chen L, Ding X, Tao R, Zhang YX, Wang JF. Hospital-acquired invasive pulmonary aspergillosis in patients with hepatic failure [serial online]. *BMC Gastroenterol*. 2008;8:32.
36. Garbino J, Rohner P, Kolarova L, Ondrusova A, Lew D. Successful treatment of pulmonary invasive aspergillosis with voriconazole in patients who failed conventional therapy. *Infection*. 2003;31:241-243.
37. Rijnders BJ, Cornelissen JJ, Slobbe L, et al. Aerosolized liposomal amphotericin B for the prevention of invasive pulmonary aspergillosis during prolonged neutropenia: a randomized, placebo-controlled trial. *Clin Infect Dis*. 2008; 46:1401-1408.
38. Kobayashi R, Kaneda M, Sato T, Ichikawa M, Suzuki D, Ariga T. The clinical features of invasive fungal infection in pediatric patients with hematologic and malignant diseases: a 10-year analysis at a single institution at Japan. *J Pediatr Hematol Oncol*. 2008;30:886-890.
39. Meersseman W, Vandecasteele SJ, Wilmer A, Verbeken E, Peetermans WE, Van Wijngaerden E. Invasive aspergillosis in critically ill patients without malignancy. *Am J Respir Crit Care Med*. 2004;170:621-625.
40. Latge JP. *Aspergillus fumigatus* and aspergillosis. *Clin Microbiol Rev*. 1999;12:310-350.
41. Sanguinetti M, Posteraro B, Pagano L, et al. Comparison of real-time PCR, conventional PCR, and galactomannan antigen detection by enzyme-linked immunosorbent assay using bronchoalveolar lavage fluid samples from hematology patients for diagnosis of invasive pulmonary aspergillosis. *J Clin Microbiol*. 2003;41:3922-3925.
42. Clancy CJ, Jaber RA, Leather HL, et al. Bronchoalveolar lavage galactomannan in diagnosis of invasive pulmonary aspergillosis among solid-organ transplant recipients. *J Clin Microbiol*. 2007;45:1759-1765.