

## Pneumocystis Carinii Pneumonia in Patients with Solid Tumors and Lymphomas: Predisposing Factors and Outcome

VASSILIOS BARBOUNIS, GEORGE APERIS, ELEFThERIOS GAMBLETSAS,  
GEORGE KOUMAKIS, MATINA DEMIRIS, MICHAEL VASSILOMANOLAKIS and ANNA EFREMIDIS

*Second Department of Medical Oncology, St. Savas Hospital, Athens, Greece*

**Abstract.** *Aim: The incidence of Pneumocystis carinii pneumonia (PCP) is increasing in patients with cancer. The possible routes of transmission in this population, as well as the epidemiological data of PCP, are not very well understood. The collection and analysis of data concerning the predisposing factors for PCP will elucidate this subject. Patients and Methods: We studied 26 patients suffering from cancer who developed PCP during the five-year period 1997-2002. Results: Twenty-one patients had a solid tumor diagnosis while the remaining five had a lymphoma. All of them received intensive combination chemotherapy, while eight of them also received high-dose therapy and bone marrow transplantation. Nineteen of our patients had long hospitalization before the onset of PCP. All of them had received corticosteroids for various reasons. Among them, many patients had been exposed to radiotherapy and, in particular, in fields which encompass the major thoracic duct. Eighteen patients survived after the initiation of appropriate treatment, while eight others succumbed. Conclusion: In this series, protracted deep lymphopenia, long hospitalization, radiotherapy and intensive chemotherapy were considered serious risk factors for developing PCP.*

*Pneumocystis carinii* is an opportunistic microorganism with wide distribution and low pathogenicity. Since the first published report in 1953 (1), *Pneumocystis carinii* pneumonia (PCP) has been described mainly in immunocompromized patients with hematological malignancies, organ transplant recipients collagen vascular disease and primary immune deficiencies or those under treatment with steroids or chemotherapy (2,3).

*Correspondence to:* Vassilios Barbounis, MD, Second Department of Medical Oncology, St. Savas Hospital, 171 Alexandra's Avenue, 115 22 Athens, Greece. Tel: 0030-210-6409415, Fax: 0030-210-6409384, e-mail: barbou@ath.forthnet.gr

*Key Words:* *Pneumocystis carinii*, pneumonia, lymphopenia, corticosteroids, radiation of thoracic duct.

Despite these reports, PCP was a rare condition until the advent of acquired immunodeficiency syndrome (AIDS) when PCP became the most common infection complicating these patients (4, 5). However, little attention has been given to PCP in patients without AIDS and, in particular, those suffering from solid tumor malignancies (6).

Additionally, great concern has arisen in the hospital community about the epidemiology and the mode of transmission of the infection, including the possibility of the emergence of new strains of *P. carinii* and nosocomial transmission with clusters of infection (7, 8) in people without evidence of predisposing factors.

With this prospective study, we sought to determine the potential risk factors for the elevated incidence of PCP observed in the department of Medical Oncology over the previous 5 years, and focus on changes in clinical practice which might account for the increase of this phenomenon in cancer patients, the contribution of each one of the above-mentioned factors to the evolution of the infection and the necessary measures to prevent the transmission of the infection.

### Patients and Methods

All patients with a diagnosis of *P. carinii* infection from 1997 to 2002, who were hospitalized in the Second Department of Oncology in "St. Savas" Hospital, Athens, Greece, were prospectively studied. Patients with known HIV infections were excluded from this analysis.

We reviewed the charts and all the relevant information concerning the demographics of the patients, the clinical findings and the putative predisposing factors. A patient was considered as a case of PCP when the clinical picture was confirmed by the presence of *P. carinii* by immunofluorescence in a sputum specimen received within 30 days of an episode.

The factors under question were the following: 1. Radiotherapy (site, field and total dose given) 2. Chemotherapy (type of agents, number of previous cycles) 3. Use of corticosteroids (dose and duration) 4. Combination of the above.

The radiotherapy charts were also reviewed to obtain information regarding the fields of radiotherapy and the total dose given as well as the time of radiotherapy given in relation to a PCP episode.

For the purpose of our study, we defined as "use of corticosteroid" if a patient received corticosteroids within 3 months of PCP diagnosis.

Table I. Patient characteristics.

	Number of patients
Male	9
Female	17
Age (median- range)	51 (25-70)
Breast cancer	10
Lung cancer	6
Two primaries	1
Non Hodgkin's lymphoma	4
Hodgkin's disease	1
Testicular cancer	2
Cervical cancer	1
Total	26

As corticosteroid tapering, we considered a decrease of the equivalent of 10 mg prednisone within the four-week period prior to diagnosis of the infection. Patients on chemotherapy, who received corticosteroid as part of their regimen and discontinued the drug abruptly, were considered as in tapering. All corticosteroid doses were converted to equivalent doses of dexamethasone.

Patients who had another episode of PCP after a period of six months were considered as a second case of *P. carinii* infection. All but one patient were treated with trimethoprim 20 mg/kg/day and sulfamethoxazole 100mg/kg/day. One patient received clindamycin and pentamidine because of an allergy to co-trimoxazole.

## Results

There were 26 cases of proven PCP. All additional patients with clinical syndrome similar to PCP, but without sufficient evidence of *P. carinii*, were excluded from this analysis. Demographic data of the patients are shown in Table I.

The median age was 51 years (range 25-70 years). The presenting symptom was fever above 38.5°C in eleven patients, shortness of breath in twenty-four and cough in twelve. The chest X-rays revealed pulmonary consolidation in four patients or alveolar and interstitial infiltrations in twenty, eighteen of them being bilateral and two unilateral. In two patients the CT scan of the lungs revealed a ground glass appearance. The arterial pO<sub>2</sub> in room air was less than 50 mmHg in one patient; ten patients had 50-69 mmHg, eleven patients 60-69 mmHg, two patients 70-79 mmHg and two patients 80-89 mmHg. The oxygen saturation was 90+ -6%.

In twenty-three patients the diagnosis was confirmed by revealing *P. carinii* in the sputum by immunofluorescence and in three by bronchoalveolar lavage. Seventeen patients had elevated serum LDH, three had normal and six unknown upon diagnosis.

All twenty-six patients had previously received chemotherapy. Eight patients had undergone high-dose chemotherapy and rescue with peripheral blood stem cells.

Table II. Chemotherapeutic regimens administered to patients with *Pneumocystis carinii* pneumonia.

Program	No. of patients
CMF	5
Anthracyclines	11
Cisplatin	14
CHOP	2
Paclitaxel/Docetaxel	12
Carboplatin/Etoposide	3
MOPP/ABVD	3
Irinotecan/gemcitabine	1

However, twelve out of twenty-six patients had received paclitaxel, docetaxel or both. Four patients had received bone marrow transplantation and taxanes. The chemotherapeutic regimens are shown in Table II.

The vast majority of our patients (22 out of 26) received radiotherapy, many of them in multiple sites. Seven of them received whole brain radiation. The radiotherapy fields are shown on Table III. Considering the length and the course of the thoracic duct, which begins from the level of L2 vertebrae and arrives at the base of the neck, it is obvious that nine patients had received radiotherapy to a portion or to the whole thoracic duct. Nineteen patients had been hospitalized during the period of 2 months preceding the manifestation of PCP in our department, while four others were home during the same period of time. There was insufficient data for three patients. At presentation of PCP, twelve patients had WBC above 4000/mm<sup>3</sup>, four patients between 3-4000/mm<sup>3</sup>, two between 2-3000/mm<sup>3</sup> and one above 500/mm<sup>3</sup>. It is important that, at the same time, six patients had lymphocytes above 1000/mm<sup>3</sup>, while nine patients had an absolute lymphocyte count (ALC) between 500-999/mm<sup>3</sup>, nine below 499/mm<sup>3</sup> and one patient below 100/mm<sup>3</sup>. The time elapsed from the beginning of chemotherapy until the manifestation of PCP was 11 years in one patient, 5 in two, 4 in two, 3 in one, 2 in two, but 18 months in five, 12 months in five, 8 months in three, 6 months in one, 4 months in one, 3 months in two and 1 month in one.

Eighteen patients received corticosteroids during the three months before the onset of PCP. Two presented with PCP but without evidence of recent use of corticosteroids, while five patients had received corticosteroids as part of their antiemetic regimen. There were no data regarding the use of corticosteroids in one patient. The cumulative dose of corticosteroids expressed in equivalent mg of dexamethasone was median 320 mg with a range from 64 to 1224 mg. The duration of corticosteroids administration before the

Table III. Irradiated fields in patients with *Pneumocystis carinii* pneumonia.

Field	No. of patients
Brain	7
Mantle	1
Inverted Y	1
Thoracic spine	5
Lumbar spine	3
Cervical spine	1
Left breast	4
Right breast	2
Mediastinum	5
Chest wall	4
Pelvic	5
Left lung	2
Spleen	1

Table IV. Risk factors predisposing to PCP.

Risk factor	No. of patients
Chemotherapy	26
Radiotherapy	22
Bone Marrow Transplantation	8
Taxanes administration	12
Mediastinal radiotherapy	9
Corticosteroids*	18
Corticosteroids tapering	9
Chemo longer than 12 months before PCP	18
Chemo less than 12 months before PCP	8
Absolute number of lymphocytes $\geq 1000$	6
500-999	9
<500	9

\*Corticosteroids administration for three months before PCP presentation

infection was median 17 days, with a range from 4 to 90 days. Nine patients were in tapering of corticosteroids use. Five developed PCP during treatment with steroids. Twelve received corticosteroids as part of their premedication of taxanes. All the possible risk factors are demonstrated in Table IV. Out of twenty-six cases diagnosed *ante mortem*-eighteen survived at least 4 weeks after PCP diagnosis and initiation of the appropriate treatment and eight died. Clinical data were comparable in both groups.

## Discussion

*Pneumocystis carinii* pneumonia remains an infrequent event among patients with solid tumors (9) or hematological malignancies. In Memorial Sloan Kettering, New York, during the period 1960-1970, only 20 cases were seen (10). De Vita described that the most common clinical setting for the development of PCP is in a patient successfully treated with combination chemotherapy, usually including steroids, for a hematological malignancy. The disease also developed in patients with solid tumors. PCP was most likely to occur during the reduction or withdrawal of chemotherapy or even during clinical remission. Sometimes patients with uncontrolled tumor growth were candidates to develop PCP (11). On the contrary, PCP is very common in patients with AIDS (12).

However, we and others (13, 14) have observed an increase in the incidence of PCP in patients without HIV infection, but with neoplastic diseases, in the last decade (15). The reason for the increasing attack rate among patients with primary or metastatic malignancies remains unclear. Possible explanations may include higher clinical suspicion, improved diagnostic techniques, increased use of immunosuppressant agents and possible altered epidemiological agents associated with *P. carinii*

In the 1980s, it was noticed, for the first time, that the increase of PCP in patients with solid tumors occurred mainly in patients with primary or metastatic brain neoplasm (16). The reason for this remains unclear and is further obscured by the fact that the vast majority of patients with primary or metastatic brain disease receive corticosteroids for a long period of time. In our group of patients, twenty-three out of twenty-six received corticosteroids for a median of 17 days (range 4-90), with a median cumulative dose of 320 mg dexamethasone (range 64-1224 mg).

Corticosteroids were given not only in the case of brain irradiation, but also as premedication before the administration of taxanes or as a part of the antiemetic regimen in combination with 5-HT<sub>3</sub> receptors antagonists. Patients under corticosteroid treatment frequently develop clinical manifestations of PCP when the corticosteroids are tapered and, as a rule, slowly deteriorate for 1-2 weeks before seeking medical advice. The vast majority of patients in all the reported series so far had been previously exposed to corticosteroids (12). Yale and Limper from the Mayo Clinic (17) reported on 116 patients with a variety of immunosuppressive disorders who developed PCP. Corticosteroids had been administered systematically to 90.5% of them one month before the diagnosis of PCP. The median daily corticosteroid dose was equivalent to 30 mg of prednisone. It is noteworthy that twenty-five of those patients had received as little as 16 mg of prednisone daily. The median duration of corticosteroids was 12 weeks before the development of PCP, but 25% of these patients had been exposed to corticosteroids for 8 weeks or less (17).

There are many chemotherapeutic agents that are associated with PCP and, in numerous reports, patients have developed PCP without receiving corticosteroids, only conventional combination chemotherapy (18-20).

Our patients, as a whole, received intensive chemotherapy consisting of anthracyclines, taxanes, irradiation and high-dose therapy, which is known to lead to severe immunosuppression (21). Half of our patients received, as a part of their conventional chemotherapy, taxanes, either paclitaxel or docetaxel, while four of them received both transplantation and taxanes. Tong and co-workers reported that taxanes affected the immune functions, docetaxel more than paclitaxel. Paclitaxel and docetaxel have an adverse effect on the lymphocyte count and this fact, in conjunction with the fact that our patients received concomitantly corticosteroids and combination chemotherapy, may play a critical role in their immunocompetence. The NK cytotoxicity is mainly decreased as well as the IL-10 serum levels (22).

The intensity of chemotherapy is a very important issue. Transplant patients are reported to be at high risk of developing PCP (23, 24). Another study demonstrated that patients undergoing autologous transplantation for breast cancer experienced a prolonged period of T cell dysfunction (25). Our patients received intensive combination chemotherapy; half of them received additional chemotherapy or underwent autologous bone marrow transplantation or both.

There are cases, however, of PCP without exposure to any of the above-mentioned factors. This fact makes the understanding of the pathogenesis of PCP more difficult.

Eighteen out of twenty-six of our patients had below  $1000/\text{mm}^3$  lymphocytes, while nine of them had fewer than  $500/\text{mm}^3$ . Severe lymphopenia was the only common factor in a cohort of patients reported by Sen *et al.* (26). More than ten patients had received irradiation, which included the thoracic duct. Radiation of the thoracic duct may contribute further to a patient's lymphopenia (27), with radiation therapy at the mediastinal area considered to be a major predisposing factor. Other investigators confirmed that radiotherapy alone, or in combination with chemotherapy, induces immunosuppression in cancer patients (28).

Very little is known about the transmission and epidemiology of *P. carinii* (29). Outbreaks of PCP have been described among immunocompromized patients (30). There is strong evidence that *P. carinii* can be transmitted from person to person (31), while in animals there is proven transmission by air (32). Other investigators have reported a dramatic increase in the incidence of PCP in non- AIDS patients when patients with neoplastic disease and patients with AIDS and PCP were treated in the same hospital (12). However, in our hospital, there were no AIDS patients during the period of this study, though in the same department there were leukemia patients, patients with lymphomas undergoing treatment and patients undergoing bone marrow transplantation, although in a different unit. All these heavily treated patients may contribute to the development of a pool of *P. carinii* microorganisms that colonize the most susceptible patients and are then transmitted person to person.

The time of development of PCP depends on the depth of immunosuppression and its duration. The issue of isolation of patients with PCP during their treatment remains open despite the elapse of some 20 years from the first time the question was raised. (33). There are observations that add to the growing concern for hospital- acquired infections including resistant *Pneumocystis carinii* and other opportunistic pathogens. The question of the possible nosocomial transmission of PCP between immunocompromized HIV sero-negative patients led some investigators to propose various practical measures to limit the risk, such as no contact between vulnerable patients, enhanced disinfection procedures and masking of the coughing PCP patients (24).

Nineteen out of twenty-six patients were admitted to our hospital before their presentation with PCP and only four of them were in the community. This is the reverse of that described by Sepkowitz *et al.* (13), when only 18% of their patients developed PCP while they were in hospital. The rest of their patients developed the infection as outpatients. Four of our patients developed the pneumonia as outpatients, as happened to patients reported by Sen *et al.* (26). In our series, we did not observe a high mortality rate as reported by others, which may be due to a higher index of suspicion and the earlier admission and treatment initiation (34).

Although it is generally believed that infection commonly occurs as a result of reactivation, it is possible that person-to-person transmission in hospital takes place. Additional explanations for the increased number of PCP observed include the increased longevity of compromised hosts, use of more aggressive antineoplastic treatment, increased popularity of bronchoscopy and bronchoalveolar lavage in patients with pneumonia, greater awareness of pneumocystis as a pulmonary pathogen and improved laboratory techniques for identification of the organism.

Apart from the use of corticosteroids, which is a well-established predisposing factor, other factors may have a major impact on the development of PCP, such as radiation of the thorax, including radiation of the lung parenchyma which produces significant parenchymal lesions (35) or radiation of the thoracic duct, which causes a decrease of the blood lymphocytes. Patients under corticosteroids treatment are especially at risk and this risk exists even in the tapering period. It would be wise for patients under long-term corticosteroids use to receive prophylaxis against *P. carinii*.

In conclusion, long hospitalization, previous thoracic irradiation, protracted use of corticosteroids, intensive chemotherapy or use of taxanes are all predisposing factors for PCP development. Prophylaxis of patients from one or more of the above predisposing factors should be carefully considered. Any patient with neoplastic disease under corticosteroids with insidious evolution of dyspnea, cough and

fever, with or without pulmonary infiltrates, should be considered as suffering from *P. carinii* pneumonia and should be treated accordingly until proven otherwise.

## References

- 1 Vanek J, Jivorec O and Luckes J: Interstitial plasma cell pneumonia in infants. *Ann Pediatr* 180: 1-21, 1953.
- 2 Walzer PP, Perl DP and Krogstad DJ: *Pneumocystis carinii* pneumonia in the United States: epidemiologic, diagnostic and clinical features. *Ann Intern Med* 80: 83-93, 1974.
- 3 Hughes WT: *Pneumocystis carinii* pneumonitis. *Chest* 84: 81-83, 1984.
- 4 Glatt AE and Chirgwin K: *Pneumocystis carinii* pneumonia in human immunodeficiency virus-infected patients. *Arch Intern Med* 150: 271-279, 1990.
- 5 Masur H, Gill VS, Ognibene FP, Shelhammer J, Godwin C and Kovacs JA: Diagnosis of *Pneumocystis pneumonia* by induced sputum technique in patients without the acquired immunodeficiency syndrome. *Ann Intern Med* 109: 755-756, 1988.
- 6 Luna MA and Cleary KR: Spectrum of manifestations of *Pneumocystis carinii* pneumonia in patients with neoplastic diseases. *Semin Diagn Pathol* 6: 262-272, 1989.
- 7 Jacobs JL, Libby DM, Winters RA, Gelmon DM, Fried ED, Hartman BJ *et al*: A cluster of *Pneumocystis carinii* pneumonia in adults predisposing illnesses. *N Engl J Med* 323: 246-250, 1990.
- 8 Walzer PD: *Pneumocystis carinii*: new clinical spectrum? *N Engl J Med* 342: 263-265, 1991.
- 9 Varthalitis J, Aoun M, Daneau D and Meunier F: *Pneumocystis carinii* pneumonia in patients with cancer. *Cancer* 71: 481-485, 1993.
- 10 Rosen P, Armstrong D and Ranos C: *Pneumocystis carinii* pneumonia: a clinicopathologic study of twenty patients with neoplastic diseases. *Am J Med* 53: 428-436, 1972.
- 11 DeVita VT Jr, Goodell B, Hubbard S, Geelhoed GW and Young RC: *Pneumocystis pneumonia* in patients with cancer: clinical setting. *Natl Cancer Inst Monograph* 43: 41-47, 1976.
- 12 Mansharamani N, Garland R, Delaney D and Koziel H: Management and outcome patterns for adult *Pneumocystis carinii* pneumonia 1985-1995. *Chest* 118: 704-711, 2000.
- 13 Sepkowitz KA, Brown AE, Telzak EE, Gottlieb S and Armstrong D: *Pneumocystis carinii* pneumonia among patients without AIDS at a cancer hospital. *JAMA* 267(6): 832-837, 1992.
- 14 Haron E, Bodey GP, Luna MA, Dekmerzian R and Elting L: Has the incidence of *Pneumocystis carinii* pneumonia in cancer patients increased with the AIDS epidemic? *Lancet* 2: 904-905, 1988.
- 15 Arend SM, Kroon FP and van't Wout JW: *Pneumocystis carinii* pneumonia in patients without AIDS 1980 through 1993: an analysis of 78 cases. *Arch Intern Med* 155: 2436-2441, 1995.
- 16 Henson JW, Jalaj JK, Walker RW, Stover DE and Fels AO: *Pneumocystis carinii* pneumonia in patients with primary brain tumor. *Arch Neurol* 48: 406-409, 1991.
- 17 Yale SH and Limper AH: *Pneumocystis carinii* pneumonia in patients without acquired immunodeficiency syndrome associated illness and prior corticosteroid therapy. *Mayo Clin Proc* 71: 5-13, 1996.
- 18 Hughes WT, Revera GK, Schell MJ, Thornton D and Lott L: Successful intermittent chemoprophylaxis for pneumocystis pneumonitis. *N Engl J Med* 316: 1627-1632, 1987.
- 19 Leff RL, Case JP and McKenzie R: Rheumatoid arthritis, methotrexate therapy and pneumocystis pneumonia. *Ann Intern Med* 112: 716, 1990.
- 20 Hardy R, Cummings C, Faulkner M and Obiany OS: *Pneumocystis carinii* pneumonia following 5-fluorouracil administration. *J Natl Med Ass* 79: 1205-1209, 1987.
- 21 Browne MJ, Hubbard SM, Longo DL, Fisher R, Wesley R, Ihde D *et al*: Excess prevalence of *Pneumocystis carinii* pneumonia in patients treated for lymphoma with combination chemotherapy. *Ann Intern Med* 104: 338-344, 1986.
- 22 Tong AW, Seamour B, Lawson JM, Ordonez G *et al*: Cellular immune profile of patients with advanced cancer before and after taxane treatment. *Am J Clin Oncol* 23: 463-472, 2000.
- 23 Santiago-Delpin EA, Mora E, Gonzales AZ *et al*: Factors in an outbreak of pneumocystis carinii in a transplant unit. *Trans Proc* 20 (Suppl 1): 462-465, 1988.
- 24 Mounib B, Cabane J, Blum I, Picard O, Wattianaux MJ and Impert JC: Risk of nosocomial *Pneumocystis carinii* pneumonia in immunosuppressed patients not infected by human immunodeficiency viruses. *Rev Med Intern* 15: 95-100, 1999.
- 25 Avigan D, Wu Z, Joyce R *et al*: Immune reconstruction following high dose chemotherapy with stem cell rescue in patients with advanced breast cancer. *Bone Mar Transplant* 26: 169-174, 2000.
- 26 Sen RP, Walsh TE, Fisher W and Brock N: Pulmonary complications of combination therapy with cyclophosphamide and prednisolone. *Chest* 99: 143-146, 1991.
- 27 Hughes WT, Feldman S, Aur RJA, Verloza MS, Hustu HO and Simone JV: Intensity of immunosuppressive therapy and incidence of *Pneumocystis carinii* pneumonia. *Cancer* 36: 2004-2009, 1975.
- 28 Santin AD, Hermond PL, Ravaggi A, Bellone S, Roman J and Pecorelli S, Cannon M and Parham GP: Effects of concurrent cisplatin administration during radiotherapy vs radiotherapy alone on the immune function of patients with cancer of the uterine cervix. *Int J Radiat Oncol Biol Phys* 48: 997-1006, 2000.
- 29 Masur H, Lane HC, Kovacs JA, Allegra C *et al*: *Pneumocystis pneumonia*: from hence to clinic. *Ann Intern Med* 111: 813-826, 1989.
- 30 Chusid MJ and Heyrman KA: An outbreak of *Pneumocystis carinii* pneumonia at a pediatric hospital. *Pediatrics* 62: 1031-1035, 1978.
- 31 Brazinsky JH and Phillips JE: *Pneumocystis pneumonia* transmission between patients with lymphoma. *JAMA* 209: 1527, 1969.
- 32 Walzer PD, Schnelle V, Armstrong D, and Rosen PP: Nude mouse: a new experimental model for *Pneumocystis carinii* infection. *Science* 197: 177-179, 1977.
- 33 Giron JA, Martinez S and Walzer PD: Should inpatients with *Pneumocystis carinii* be isolated? *Lancet* 2 (8288): 46, 1982.
- 34 Nuesch R, Bellini C and Zimmerli W: *Pneumocystis carinii* pneumonia in human immunodeficiency virus (HIV)-positive and HIV-negative immunocompromized patients. *Clin Infect Dis* 29: 1519-1523, 1999.
- 35 Nieder C, Jeremic B, Astner S and Molls M: Radiotherapy-induced lung toxicity: risk factors and prevention strategies. *Anticancer Res* 23(6D): 4991-4998, 2003.

Received July 21, 2004

Revised December 21, 2004

Accepted December 28, 2004