Pneumocystis carinii pneumonia in patients with malignant haematological diseases: 10 years' experience of infection in GIMEMA centres

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Summary. A retrospective survey was conducted over a 10-year period (1990–99) among 52 haematology divisions in order to evaluate the clinical and laboratory characteristics and outcome of patients with proven *Pneumocystis carinii* pneumonia (PCP) complicating haematological diseases. The study included 55 patients (18 with non-Hodgkin's lymphoma, 10 with acute lymphoblastic leukaemia, eight with acute myeloid leukaemia, five with chronic myeloid leukaemia, four with chronic lymphocytic leukaemia, four with multiple myeloma, three with myelodysplastic syndrome, two with myelofibrosis and one with thalassemia) who developed PCP. Among these, 18 (33%) underwent stem cell transplantation; only two received an oral prophylaxis with trimethroprim/sulphamethoxazole. Twelve patients (22%) developed PCP despite protective isolation in a laminar airflow room. The most frequent symptoms were: fever (86%), dyspnoea (78%), non-productive cough (71%), thoracic pain (14%) and chills (5%); a severe hypoxaemia was present in 39 patients (71%). Chest radiography or computerized tomography showed interstitial infiltrates in 34 patients (62%), alveolar infiltrates in 12 patients (22%), and alveolar–interstitial infiltrates in nine patients (16%). Bronchoalveolar lavage was diagnostic in 47/48 patients, induced sputum in 9/18 patients and lung biopsy in 3/8 patients. The diagnosis was made in two patients at autopsy. All patients except one started a specific treatment (52 patients trimethroprim/sulphamethoxazole, one pentamidine and one dapsone). Sixteen patients (29%) died of PCP within 30 d of diagnosis. Multivariate analysis showed that prolonged steroid treatment ($P < 0.006$) and a radiological picture of diffuse lung involvement ($P < 0.003$) were negative diagnostic factors.

Keywords: leukaemia, lymphoma, *Pneumocystis carinii*, pneumonia.

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Pneumocystis carinii pneumonia (PCP) is an important cause of morbidity and mortality in immunocompromised patients (Thomas & Limper, 1998). Although PCP is frequently

associated with acquired immunodeficiency syndrome (AIDS), several groups of non-AIDS immunocompromised patients are also at risk of PCP (Smulian *et al*, 1993; Delmas *et al*, 1995; Lee *et al*, 1996). These include patients with solid tumours, those undergoing organ transplantation or patients suffering from inflammatory conditions requiring chronic immunosuppression with corticosteroids or cytotoxic agents such as purine analogues (Kovacs *et al*, 1984; Yale & Limper, 1996).

In the past, the clinical characteristics and treatment outcome of PCP in patients with haematological malignancies have been widely described (Rosen *et al*, 1972; Walzer *et al*, 1974; Ruebush *et al*, 1978; Peters *et al*, 1987; Sepkowitz, 1993; Varthalitis *et al*, 1993; Arend *et al*, 1995). However, at present, the use of new chemotherapies, characterized by prolonged and deep immunosuppression, has modified the epidemiology and outcome of this group of patients.

On the basis of these considerations, in this retrospective analysis we reviewed, in a multicentric study, the records of 55 patients affected by haematological malignancies, who developed proven PCP between 1990 and 1999, in order to evaluate the underlying disorder, the clinical presentation and the factors that influenced the outcome.

PATIENTS AND METHODS

We retrospectively collected all cases of microbiologically and/or histologically documented PCP in adult patients (> 12 years of age) with haematological malignancies observed between January 1990 and December 1999 in 52 GIMEMA (Gruppo Italiano Malattie EMatologiche dell'Adulto) centres.

Diagnosis of PCP was proved, confirming the clinical and radiological suspicion, on the basis of microbiological or histological evidence of *Pneumocystis carinii* by:

- visualization of *P. carinii* (PC) trophozoites (trophic form) from sputum or bronchoalveolar (BAL) fluid, using either a modified Wright–Giemsa or a Papanicolaou stain, and cysts stained with toluidine blue O stain (Naimey & Wuerker, 1995) and/or
- polymerase chain reaction (PCR), from induced sputum and BAL fluid, using primers for the human *P. carinii* mitochondrial large-subunit (mtLSU) rRNA gene (Antinori *et al*, 1995) and/or
- immunostaining using monoclonal antibodies (mAbs) for human *P. carinii* in sputum, nasopharyngeal aspirates, BAL fluid or lung tissue obtained by transbronchial biopsy or open lung biopsy (Kovacs *et al*, 1988) and/or
- histological documentation of tissue invasion by PC cysts or trophozoites in lung tissue obtained by transbronchial biopsy or by open lung biopsy or at autopsy (Thomas & Limper, 1998).

Patients not meeting these criteria were excluded from the study.

Hospital records of patients with PCP were reviewed to evaluate demographic data (age, sex), type and stage of underlying haematological disease, antibiotic PC prophy-laxis in the 30 d before diagnosis of PCP and all types of treatment (e.g. steroids and cyclosporine).

Prophylaxis against PC was not standardized in all centres participating in the study. An oral prophylaxis with trimethoprim–sulphamethoxazole (TMP/SMZ) was administered twice daily two or three times a week only for patients with lymphoproliperative disorders (excluding Hodgkin's disease) and in those patients who underwent allogeneic bone marrow transplantation.

The type of drugs employed, the total doses and duration of treatment for PCP were also recorded. Patients had a median follow-up of 100 d after the microbiological diagnosis of PCP. Mortality was judged as due to PC when death occurred within 30 d of diagnosis as a result of respiratory insufficiency and/or related complications. Autopsy was carried out in nine patients only.

All patients were included in charts compiled by two of the authors with particular experience of the subject. All data were coded and stored in a computerized database.

Statistical methods. Definitions and end-points of the study were agreed upon prior to chart examination. Data were analysed by descriptive statistical methods and differences between groups were calculated using χ^2 test or Fisher's exact test if appropriate.

Factors affecting infection outcome (death versus no death) were investigated using a stepwise backward method and were excluded from the model when the probability was higher than 0·1. Results are presented as odds ratios [OR, with 95% confidence intervals (CI)].

The best cut-off of continuous variables (age, steroid dose, days on steroids, neutrophil count, lymphocyte count, Po_2 level) was ascertained empirically using correlation coefficients.

Probability of events was obtained using the Kaplan–Meier method and the groups were compared by the log-rank test. Significance was established at $P < 0·05$ (two sided). Data were analysed using the Statistical Package for the Social Sciences (SPSS, Chicago, IL, USA).

RESULTS

The clinical and laboratory characteristics of the 55 patients with PCP are reported in Table I, while in Table II the underlying diseases and the phases of their treatment are shown.

Epidemiological data

During the study period, 55 patients with haematological diseases were diagnosed with documented PCP.

The lack of a national register did not allow the incidence of PCP to be calculated for each group of haematological malignancies. However, such an evaluation was feasible for patients with acute leukaemia admitted to the centres involved in the study, as well as for patients undergoing bone marrow transplantation (BMT). An infection due to PC was demonstrated throughout the course of disease in 12 out of 2171 new cases of adult acute leukaemia (0·5%).

The incidence of proven PCP in transplanted patients was calculated on the basis of the data from the Gruppo Italiano

Table I. Main clinical and laboratory features of 55 patients with PCP observed between 1990 and 1999 in 52 centres.

Patients	
Sex (males/females)	38/17
Median age (years; range)	47 (15–78)
Underlying haematological disease	
NHL	18
ALL	10
AML	8
CML	5
MM	4
CLL	4
MDS	3
IMF	2
TAL	1
Environmental isolation (air laminar flow)	12/55
Kind of treatment	
Chemotherapy	44/55
Immunosuppressive treatment	11/55
Transplantation	
Allogeneic	12
Autologous	3
PBSC	3
Steroid treatment	39/55
No. of patients	
Median total dosage of methyl-prednisolone (mg; range)	2200 (88–22 500)
Median treatment duration (days; range)	35 (3–1540)
Previous antibiotic treatment	31/55
Median duration antibiotics (days; range)	10 (2–30)
Fever	46/55
Neutrophil count at the onset of infection ($< 1 \times 10^9/l/> 1 \times 10^9/l$)	12/43
Lymphocyte count at the onset of infection ($< 1 \times 10^9/l/> 2 \times 10^9/l$)	33/22
Hypoxaemia ($Po_2 < 70$ mmHg)	39/55
Chest radiograph/CT scan	34/55
Interstitiopathy	21/55
Interstitiopathy + alveolar	
Trimethoprim–sulphamethoxazole prophylaxis	2/55

NHL, non-Hodgkin's lymphoma; ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CML, chronic myeloid leukaemia; MM, multiple myeloma; CLL, chronic lymphocytic leukaemia; MDS, myelodysplastic syndrome; IMF, idiopathic myelofibrosis; TALm, thalassaemia.

Trapianto di Midollo Osseo (GITMO) Registry (unpublished data). Only 14/3741 (0·3%) patients were undergoing allogeneic BMT and 5 out of 6597 (0·07%) submitted to autologous BMT or autologous peripheral blood stem cell transplantation (PBSCT) developed a PCP.

Patients' characteristics
Patients' age ranged between 15 and 78, with a median of 47 years, and a prevalence of males over females (38 versus 17) was observed.

The underlying haematological malignancies of patients at the time of PCP diagnosis and the phase of treatment are reported in Table I. Lymphoproliferative diseases represented 58% of cases (32 patients), non-Hodgkin's lymphoma (NHL: 18 patients, 33%) and acute lymphoblastic leukaemia (ALL: 10 patients, 18%) being the most frequent malignancies observed. One patient, affected by β-thalassaemia and undergoing allogeneic bone marrow transplantation was included in the study.

Considering the stage of the haematological diseases, in the majority of cases, PCP (23 episodes, 42%) was documented in patients who were in complete remission.

The latency between the diagnosis of the haematological disease and PCP infection had a high variability and ranged from 1 to 128 months (median 5 months).

Eighteen patients (22%) underwent BMT (allogeneic or autologous). The median interval between transplantation and the diagnosis of PCP was 180 d (range 10–330).

Chemotherapy and immunosuppressive treatment
Before the onset of PCP, 44/55 patients (80%) had been treated with chemotherapy and 11/55 patients (20%) had received immunosuppressive treatment.

Chemotherapy included cyclophosphamide in 15 patients and cytarabine (Ara-C) in 10 patients. Only two patients had been previously treated with purine analogues: one patient with 2- chlorodeoxyadenosine and another with fludarabine. Five patients were treated with cyclosporin A (CyA) in association with steroids, while one patient received CyA alone. Thirty-nine patients (57%) had a history of previous treatment with corticosteroids at a median equivalent daily dose of 50 mg (range 8–150) of 6-methyl-prednisolone for a median time of 35 d (range 3–1540), with a median total dose of 2200 mg (range 88–22 500).

At the onset of infection, 12 patients (22%) were neutropenic (neutrophil count lower than $1 \times 10^9/l$) and 33 patients (60%) had a lymphocyte count lower than $1 \times 10^9/l$. An inversion of the CD4/CD8 ratio was observed in 5 of 10 available cases.

Prophylaxis
Only 2 of 55 patients who developed PCP had received prophylaxis with TMP/SMZ. The duration of prophylaxis before the diagnosis of PCP was in one case 80 d and in one case 270 d.

Twelve patients (22%) developed PCP despite protective isolation in a laminar airflow room.

Clinical presentation and diagnostic procedures
The signs and symptoms related to PCP became apparent in 42 patients (76%) after discharge. In the case of 13 patients (27%), PCP occurred during hospitalization after a median of 38 d from admission (range 15–212).

The onset of symptoms was not uniform: in 39 cases it was fulminate and characterized by high-grade fever and severe hypoxaemia, while in 16 patients the presentation was subacute with the onset of progressive dyspnoea, a non-productive cough and a low-grade fever over several weeks. Fever, which was present in 84% of episodes, was the most frequent symptom.

Table II. Haematological malignancy and phase of treatment of 55 cases of PCP.

	AML	ALL	NHL	CML	MM	CLL	MDS	IMF	TAL	Total (%)
Induction/reinduction	2	1	10	–	1	1	1	–	–	16 (29)
Consolidation	1	1	–	–	–	–	–	–	–	2 (3,6)
Maintenance	1	5	–	–	–	3	–	1	–	10 (18)
Autologous BMT	–	–	3	–	–	–	–	–	–	3 (5,5)
Allogeneic BMT										
Conditioning	2	1	–	1	–	–	–	–	–	12 (22)
Immunosuppression	1	1	–	4	2	–	–	–	–	
PBSCT	–	–	1	–	1	–	–	–	1	3 (5,5)
Salvage	1	1	2	–	–	–	–	–	–	4 (7,2)
Immunosuppression	–	–	1	–	–	–	–	–	–	1 (2)
None	–	–	1	–	–	–	2	1	–	4 (7,2)
Total	8	10	18	5	4	4	3	2	1	55

AML, acute myeloid leukaemia; ALL, acute lymphoid leukaemia; NHL, lymphoma; CML, chronic myeloid leukaemia; MM, multiple myeloma; CLL, chronic lymphocytic leukaemia; MDS, myelodysplastic syndrome; IMF, idiopathic myelofibrosis; TAL, thalassaemia.

Empirical broad-spectrum antibiotics (a β-lactam plus an amino glycoside with or without glycopeptides) had been administered in 31 cases (56%) for a median time of 10 d (range 2–30) before the diagnosis of PCP was confirmed.

Interestingly, in nine patients (16%), a pulmonary infection due to other pathogens was diagnosed before diagnosis of PCP: four patients had cytomegalovirus (CMV) pneumonia, diagnosed by positive serology; and five patients had clinically and radiologically documented pneumonia of unknown origin. Five of these patients (55%) died within a median of 20 d from diagnosis of PCP (range 11–30).

Other symptoms and signs were: dyspnoea (78%), non-productive cough and crackles (71%), thoracic pain (14%) and chills (5%). The interval between the onset of symptoms and PCP diagnosis ranged from 2 to 5 d.

At admission the median values of arterial blood gas analysis of 42 patients performed at room air were: Po_2 57 mmHg (range 31–93), Pco_2 32 mmHg (range 23–41) and pH 7·46 (range 7·24–7·52). Severe hypoxaemia (arterial oxygen tension lower than 70 mmHg) was present in 39 patients (71%).

A diagnosis of PCP was made *in vivo* in 53 patients (96%), while in the remaining two patients (3·6%) the clinical suspicion of PCP was confirmed at autopsy only.

Standard chest radiography showed unequivocal pulmonary parenchyma abnormalities in all patients. In 34 patients (75%), bilateral infiltrates were observed, while in 21 patients (25%) unilateral infiltrates were present. In particular, a pattern of interstitial infiltrates was the most common feature [34 patients (62%)], while radiography showed alveolar infiltrates in 12 patients (22%) and both interstitial and alveolar patterns in nine patients (16%). Chest computerized tomography (CT) was performed in 20 cases, within 72 h of readiography, and confirmed the findings shown by standard radiographs.

Nine of 18 patients studied tested positive for *Pneumocystis carinii* on a stain of pulmonary secretions obtained from induced sputum.

Bronchoscopy with BAL was performed in 48 patients (87%) and was diagnostic for PCP in all but one patient. This procedure was performed within 3 d of the onset of symptomatology.

PCR analysis was performed on BAL from seven patients only and it was positive in each case. In one case, with negative stains, this enabled the diagnosis of PCP.

Transthoracic or transbronchial biopsy was performed on eight patients, but histological documentation of lung invasion by PC was documented in three patients only (37%).

The summary of the diagnostic procedures is shown in Table III.

Treatment and outcome
In all but one patient, radiological and clinical findings prompted empirical treatment for PCP, which was started within 48 h of the onset of symptoms; 52 patients were treated with high-dose i.v. TMP/SMZ at a median daily dose

Table III. Procedures that allowed diagnosis in 55 patients with proven PCP.

	BAL	BAL + induced sputum	BAL + lung biopsy	Induced sputum	Autopsy
Cases	41*	3	3	6†	2

*In one patient with negative stains, diagnosis was made by PCR on bronchoalveolar lavage fluid.
†In one patient, diagnosis of PCP was confirmed at autopsy.
BAL, bronchoalveolar lavage.

of 3·6 g (range 1·2–9·6) [3 g of sulphamethoxazole (range 1–8) and 0·6 g of trimethoprim (range 0·2–1·6)]. The total median dose of i.v. TMP/SMZ administered was 43·2 g (range 1·4–240) [36 g of sulphamethoxazole (range 1·2–200) and 7·2 g of trimethoprim (range 0·2–40)], and the median duration of therapy was 15 d (range 1–53). Patients who improved after endovenous treatment continued oral TMP/SMZ therapy with a median cumulative dose of 33·6 g (range 7·7–92·8) [28 g of sulphamethoxazole (range 6·4–77·3) and 5·6 g of trimethoprim (range 1·3–15·5)] for a median of 14 d (range 4–29) further. The overall median duration of treatment (i.v. plus oral) was 30 d (range 11–67).

Four patients unresponsive to the treatment with TMP/SMZ, at a median of 12 d (range 8–30), received pentamidine. Three of these patients died of PCP despite pentamidine treatment.

Two other patients intolerant of TMP/SMZ received pentamidine or dapsone.

Corticosteroids were given to 18 patients (36·5%) during anti-*Pneumocystis* treatment. Methyl-prednisolone (50–80 mg/d) was added to a total median dose per patient of 770 mg (range 90–23 100) for an average of 12 d (range 1–53). Among these patients, 14 were already being treated with methyl-prednisolone for the underlying disease.

Treatment failure occurred in 20 patients; 16 patients died from complications related to PCP within 30 d of diagnosis and four patients died within 60 d. A previous pulmonary infection had been already diagnosed in four of them (three CMV, and one clinical and radiological pneumonia), even if this was not considered the main cause of death.

Twenty-three patients (42%) were transferred to the intensive care unit (ICU) for respiratory failure necessitating mechanical ventilation and 14 of them (61%) died.

Among the other 35 patients (62%) a clinical improvement was observed. Six patients died within 30 d from other causes: three patients died from the underlying haematological disease (one patient had graft-versus-host disease, one a CMV infection and one a brain haemorrhage). All diagnoses were confirmed at autopsy.

One patient, affected by NHL, presented a second PCP infection 5 years after the first episode. This patient did not receive a specific prophylaxis because she suffered from TMP/SMZ allergy and refused any other prophylaxis. She died 18 d after diagnosis, despite appropriate treatment.

Factors related to mortality
At multivariate analysis, absolute lymphocytopenia, hypoxia at admission, presence of alveolar infiltrates at chest radiography and a prolonged use of corticosteroids were significantly correlated with a higher mortality from PCP (Table IV). Other parameters such as age, sex, underlying haematological malignancies, transplantation procedures, hospitalization in hepafiltered rooms, chemotherapy, use of corticosteroids and neutropenia did not influence mortality.

DISCUSSION

Pulmonary infections represent a major diagnostic and therapeutic challenge in patients with haematological malignancies. Usually, pneumonia is caused by Gram-negative agents (i.e. *Pseudomonas* spp.) or by filamentous fungi (i.e. *Aspergillus* spp. or Mucorales) (Khardori *et al*, 1990; Pagano *et al*, 1997, 1998, 1999; Patterson *et al*, 2000). The characteristics of PCP have been illustrated either for patients treated with immunosuppressive treatment or for those with AIDS (Rosen *et al*, 1972; Walzer *et al*, 1974; Ruebush *et al*, 1978; Peters *et al*, 1987; Sepkowitz, 1993; Varthalitis *et al*, 1993; Arend *et al*, 1995). However, the introduction of new drugs for the treatment of haematological malignancies (i.e. purine analogues) and the availability of innovative diagnostic tools (i.e. PCR) that can improve the sensitivity of both invasive and non-invasive diagnostic procedures might have changed the epidemiology of this complication.

It has been reported that PCP has a high incidence in preterm infants, and is especially frequent in children and adolescents with ALL, when compared with adults. Children and infants actually seem to be at high risk of PCP in the context of immunosuppression caused either by the underlying malignancy or by pharmacological agents (Russian & Levine, 2001). However, PCP has also been reported as a cause of infant pneumonia in otherwise immunocompetent infants. Serological surveys in fact indicate that the great majority of healthy, immunocompetent infants (85%) have a primary symptomatic *Pneumocystis carinii* infection before 3 years of age, suggesting that this is among the most common infections in paediatric patients (Vargas *et al*, 2001). The current belief is that the primary infection in a competent host is asymptomatic or causes an overt respiratory illness, with clinical manifestations that are different from and less severe than those known to occur in the compromised host. PCP could represent a reactivation of a latent infection, becoming manifest when the immunological defences are compromised by a haematological malignancy.

Before the general introduction of TMP/SMZ prophylaxis, the incidence of PCP was more than 20% in some centres (e.g. St Jude/Memphis and Berlin), depending on the intensity of chemotherapy and duration of steroid treatment (Hughes *et al*, 1977). Later, Hughes *et al* (1987) demonstrated, in a prospective randomized study of children with acute lymphoblastic leukaemia, the same efficacy of intermittent TMP/SMZ prophylaxis and continuous administration. Criteria for prophylaxis in adults without AIDS, in particular those with haematological malignancies, have not in contrast to the situation in children (Groll *et al*, 2001), been established in prospective controlled trials.

In this survey, we analysed the records of a large series of patients with haematological malignancies and proven PCP; these records were collected during a 10-year period from Italian Haematological departments affiliated to the GIMEMA Infection programme. Our study was retrospective, starting from the diagnosis of PCP. Owing to the lack of a common national registry for all haematological malignancies, we were not able to calculate the incidence of PCP in each category of patients; however, we were able to calculate the incidence of PCP in patients with acute leukaemia and those who underwent BMT.

Table IV. Univariate and multivariate analysis of clinical and laboratory characteristics in relation to mortality due to PCP.

Characteristics	Death from PCP/total (%)	Univariate analysis P-value	Multivariate analysis P-value
Age			
< 50 (years)	12/33 (36)	1	NS
> 50 (years)	8/22 (36)		
Sex			
Male	12/38 (31·5)	0·3	NS
Female	8/17 (47)		
Underlying disease			
Myeloprolipherative	6/18 (33)	0·7	NS
Lymphoprolipherative	14/37 (38)		
Disease stage			
CR	8/24 (33)	0·7	NS
Other	12/31 (44)		
Therapy			
Chemotherapy	17/44 (39)	0·7	NS
Immunotherapy	3/11 (27)		
Allogeneic BMT			
Yes	7/12 (58)	0·096	NS
No	13/43 (30)		
Steroids			
Yes	17/40 (42·2)	0·1	NS
No	3/15 (20)		
Steroids dosage			
< 1000 (mg)	9/29 (31)	0·4	NS
> 1000 (mg)	11/26 (42)		
Steroids duration			
< 15 d	6/28 (21)	0·02	0·0062 (OR = 2·8; CI = 2·0–3·6)
> 15 d	14/27 (52)		
Neutropenia			
< 1×10^9/l	5/12 (42)	0·7	NS
> 1×10^9/l	15/43 (35)		
Lymphopenia			
< 1×10^9/l	17/35 (48·5)	0·01	0·003 (OR = 3·1; CI 95% = 2·2–4·0)
> 1×10^9/l	3/20 (15)		
Hypoxia (mmHg)			
< 70	17/39 (43·5)	0·08	0·0039 (OR = 3·4; CI 95% = 2·4–4·4)
> 70	3/16 (19)		
Chest radiography			
Interstitiopathy	8/34 (23·5)	0·01	0·0034 (OR = 2·9; CI 95% = 2·1–3·8)
Interstitiopathy + alveolar	12/21 (57)		
Therapy			
Yes, with steroids	8/22 (36)	1	NS
Yes	12/33 (36)		

OR, odds ratio; CI, confidence interval; CR, complete remission.

As previously reported, patients with lymphoprolipherative disorders and those undergoing transplantation received intermittent prophylaxis. We have shown that the occurrence of this complication is very rare in these groups of patients, when compared with other opportunistic infections such as aspergillosis or candidaemia (Pagano *et al*, 1997, 1998, 1999; Patterson *et al*, 2000).

PCP occurs more frequently in patients with lymphoproliferative disorders, although it has been observed in patients with myelodysplatic syndromes (MDS) or acute myeloid leukaemia (AML) not receiving BMT (Peters *et al*,

1987; Varthalitis *et al*, 1993; Arend *et al*, 1995). Interestingly, we did not observe PCP in patients with Hodgkin's disease (HD), in contrast to data reported by Sepkowitz (1993). This discrepancy could be due to the lack of steroid use in our own HD trials. Another interesting fact is the absence of correlation between PCP and use of fludarabine in our patients.

It has been demonstrated that purine analogues may be associated with long-lasting T-cell lymphocytopenias, which are considered a risk factor for the occurrence of opportunistic infections caused by organisms such as *Pneumocystis*

carinii, *Listeria monocytogenes* and fungi (Wijermans *et al*, 1993; Byrd *et al*, 1995). The use of purine analogues in Italy increased after 1995 but, despite the frequent use of these drugs in all participating centres, we observed only two cases of PCP in patients treated with purine analogues (2-chlorodeoxyadenosine in one case and fludarabine in the other).

Our data are in agreement with those of Anaissie *et al* (1998), who demonstrated that fludarabine used alone did not increase the incidence of PCP in a large series of CLL patients, while a consistent number of PCP or listeriosis cases were observed when fludarabine was used in association with steroids. However, other authors did not attribute a critical role to steroids in the development of PCP (Arend *et al*, 1995).

In our study, the diagnosis of PCP using microbiological techniques was very efficient. However, surgical biopsy, which generally represents one of the most useful tools for the diagnosis of uncertain pulmonary lesions, was not as useful. This was probably as a result of either a delay in the procedure, which was determined by the critical condition of the patient, or failure to reach the site of infection.

The widely held belief that PCP is a rare disease in patients with haematological malignancies, in contrast to patients with AIDS, may explain why oral prophylaxis against PC with TMP/SMZ was not routinely used in most participating centres for all cases of haematological malignancies, particularly for myeloproliferative diseases. However, because of the low number of cases of PCP observed, we would not suggest a more diffuse prophylaxis in these patients.

Despite a timely empirical treatment with TMP/SMZ based on clinical findings and radiological pictures, we observed a considerable mortality rate (29%), which was higher than that observed in patients with AIDS (10–20%), but in agreement with other experiences (Arend *et al*, 1995; Yale & Limper, 1996). The combination of TMP/SMZ with high-dose steroids did not modify the outcome. Interestingly, in our series the specific PCP treatment was longer than that reported by other authors in AIDS (Castro, 1998). This was probably because haematological and other cancer patients presented, in contrast to HIV patients, a greater degree of lung inflammation due to poorer oxygenation and, therefore, needed prolonged treatment (Limper *et al*, 1989).

Coexisting pulmonary infections (i.e. CMV) have been frequently reported and correlated with a high mortality rate (Wang *et al*, 1970; Stover *et al*, 1985; Peters *et al*, 1987). This is confirmed in our patients. In fact, 55% of patients with PCP and a previous or concomitant bacterial or viral pulmonary infection died within 30 d of the diagnosis of PCP.

When analysing some parameters influencing the outcome of our patients, hypoxia, a more extensive pulmonary impairment and lymphopenia were found to be independent risk factors for mortality in the multivariate analysis. Interestingly, the outcome was not influenced either by the cumulative or by the daily dose of steroids, whereas the duration of steroid treatment before the onset of the complication appeared to be correlated with a worse prognosis.

Unfortunately, we were able to document CD4/CD8 ratio in only a few patients, and it was inverted in 50% of them.

In conclusion, PCP represents a rare but potentially lethal complication in patients with haematological malignancies. It is characterized by a sudden and progressive course with a more severe prognosis with respect to that of PCP in AIDS. Frequently, the prompt initiation of a specific therapy with TMP/SMZ does not change the outcome.

Prophylaxis of PCP is not widely used, but the low number of patients who developed PCP without having a lymphoproliferative disease or without having received an allogeneic transplantation does not justify the use of prophylaxis in other patient categories (i.e. AML). Further, prospective studies on a larger number of patients are necessary to confirm our epidemiological data.

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