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Acute Leukemias

Incidence and outcome of pneumonia in patients with acute leukemia receiving first induction therapy with anthracycline-containing regimens

FAUSTO ROSSINI, MAGDA VERGA, PIETRO PIOLTELLI, GIUSEPPE GILTRI,* VIVIANA SANCASSANI, ENRICO M. POGLIANI, GIANCARLO CORNEO

*Hematology Division, and *Microbiology Service, New Hospital S. Gerardo, University of Milan, Monza, Italy*

ABSTRACT

Background and Objectives. **Even though the risk of pneumonia is higher in patients with advanced disease, the potential risk of death is particularly relevant during induction therapy, when patients can be potentially cured of their hematologic disease: our study was aimed at evaluating the risk and outcome of pneumonia in these patients.**

Design and Methods. **We retrospectively studied all 458 patients affected by acute leukemia receiving an anthracycline-containing induction regimen in the years 1984-1989.**

Results. **Of the 458 patients, 109 (23.8%) developed pneumonia: 91 had acute myelogenous leukemia (AML) and 18 had acute lymphoblastic leukemia (ALL). At univariate analysis, advanced age, AML and total blast count significantly correlated with the risk of pneumonia. At multivariate analysis, only age ($p<0.0001$) and total blast count ($p=0.002$) retained their prognostic significance. Pneumonia responded to treatment in 67 (61.5%) patients, while 42 (38.5%) patients died. Among patients with pneumonia, 51 (46.8%) patients achieved a complete remission: 9/18 ALL and 42/91 AML. At univariate analysis, the most significant determinant of a positive outcome was the achievement of complete remission; a higher absolute neutrophil count at the onset of pneumonia, the absence of rales, a single infiltrate and the absence of microbiological demonstration of infection were also related to a positive outcome. At multivariate analysis, the achievement of complete remission and, with borderline significance, a single infiltrate maintained their prognostic value.**

Interpretation and Conclusions**. Pneumonia remains one of the most relevant risks of morbidity and mortality during induction therapy for acute leukemia. A fatal outcome is associated, in most cases, with a failure to achieve remission of leukemia.**

Key words: acute leukemia, pneumonia, anthracyclines, immunocompromised host, antibiotic therapy

Correspondence: Fausto Rossini, M.D., Divisione di Ematologia, Nuovo Ospedale S. Gerardo, 20052 Monza, MI, Italy. Phone: international +39-039-2333437 – Fax: international +39-039-2333440 – E-mail · ematologia@Infinito.it

Pneumonia is one of the most frequent life-threatening complications in patients affected by a hematologic neoplasia.[1-7] Although neutropenia is the most important predisposing factor, other mechanisms play a role in different settings: defects in humoral and cellular immunity, defects in mucosal defensive mechanisms, and functional alterations of neutrophils. The prognosis remains poor, even after the recent improvements in supportive therapy. The diagnosis can be difficult for many reasons:[8] an impaired inflammatory response can reduce clinical or radiological signs; an etiological diagnosis is difficult to obtain because of the risk of hemorrhage due to thrombocytopenia. Even though patients with advanced hematologic disease have a higher risk of developing pneumonia, this complication frequently affects patients with hematologic diseases at their onset. Pneumonia can be a significant cause of death in these patients, too. This study was designed to evaluate risk factors for and outcome of pneumonia in a relatively homogeneous group of patients: patients with newly diagnosed acute leukemia, treated with conventional therapeutic regimens containing anthracyclines.

Design and Methods

Patients

Patients with newly diagnosed *de novo* acute leukemia, treated from 1984 to 1999 with anthracycline-containing regimens were included. Patients who developed pneumonia during induction therapy were compared with patients who did not develop pneumonia. The study included 458 patients: 343 had acute myelogenous leukemia (AML) and 115 had acute lymphoblastic leukemia (ALL).

Induction chemotherapy

Of the 343 patients with AML, 180 were treated with idarubicin and 163 with daunorubicin; they all, except 48 patients affected by acute

promyelocytic leukemia, received cytosine arabinoside (ara-c): 25 of them received ATRA. In 74 patients the regimen included etoposide (VP-16), in 19 thioguanine, in 6 etoposide + thioguanine. Patients aged under 65 years old received three days of anthracycline and seven days of ara-c; patients aged more than 65 years received two days of anthracycline and five days of ara-c. VP-16 was given for three days. Of the ALL patients, 67 were treated with idarubicin and 48 with daunorubicin; they all received vincristine and prednisone. In 73 patients the regimen included also L-asparaginase, in 23 patients cyclophosphamide. Two different regimens were employed, with anthracyclines on days 1 and 2 or on days 1 and 8.

Assessments

Blood was taken from all patients at least every other day for routine biochemistry and hematology evaluations. Chest X-ray was performed when fever appeared and twice a week in case of persistence of fever. Three blood cultures were performed at the onset of fever and once a day until the fever abated. Bronchoalveolar lavage (BAL) or lung biopsies were not performed systematically, but were done in selected patients.

Diagnosis and definition of pneumonia

Pneumonia was defined as a new infiltrate on chest X-ray, accompanied by a fever higher than 38°C. The onset of pneumonia was defined as occurring on the day when the new lung infiltrate appeared; the end of pneumonia was defined as occurring on the day of the first normal chest X-ray or the day of the patient's death. A micro-organism was considered causative when it was isolated from the lung by bronchoalveolar lavage or biopsy or from blood (two positive blood cultures were required for *Staphylococcus epidermidis*). Cases of pulmonary edema, demonstrated leukemia infiltrates or pulmonary hemorrage were excluded. Computerized axial tomography (CAT) of the chest was performed only in selected cases prior to 1994; from 1994 it was performed systematically.

Antibiotic prophylaxis and therapy

All neutropenic patients received antibacterial prophylaxis with trimethoprim-sulfamethoxazole (one double strength tablet orally twice a day) before 1993 and with ciprofloxacin (500 mg twice a day) starting from 1993. Selected patients received antifungal prophylaxis with different drugs (nystatin, fluconazole, itraconazole, low-dose intravenous amphotericin). Most patients were treated empirically with an antibiotic combination containing an aminoglycoside (generally amikacin) and a cephalosporin. Subsequent modifications of antibacterial drugs were dictated by microbiological or clinical criteria. Intravenous amphotericin at therapeutic doses was introduced in 51 patients at a median of 7.5 days from the onset of the pneumonia. Starting from 1994, lipid formulations of amphotericins were used in selected patients; in most of these patients we used liposomal amphotericin.

Supportive therapy

Growth factors (G-CSF) were used in most patients starting from 1995. No patient received white blood cell transfusions. Platelet transfusions were given when the platelet count was lower than 5,000 or in case of hemorrhage.

Statistical analysis

T-test and Fisher's exact test were used, as appropriate.

Results

Risk of pneumonia

Tables 1, 2a and 2b detail the characteristics of the whole group of patients treated with induction therapy for acute leukemia, divided in two subgroups: patients who developed pneumonia and patients who did not.

Table 1 shows general characteristics. Tables 2a and 2b show cases of pneumonia according to FAB subtypes. Table 3 shows the time intervals between the beginning of chemotherapy and the onset of pneumonia. One hundred and nine patients developed pneumonia during induction therapy: 91 had AML and 18 had ALL.

Table 1. Characteristics of all patients with acute leukemia.

	Pneumonia	*No pneumonia*	*P*
Pts	109	349	
Age in years, mean, range	55.73 (19-80)	46.90 (18-83)	0.0001
AML, n (%)	91 (26.5%)	252 (73.5%)	
ALL, n (%)	18 (15.6%)	97 (84.4%)	
Sex M n (%)	60 (23%)	201 (77%)	n.s.
Sex F n (%)	49 (24.9%)	148 (75.1%)	
Hemoglobin g/dL, mean, range	8.68 (5.2-13.4)	9.12 (3.6-15.5)	n.s.
RBC, mean, range	2.76 (1.36-5.97)	2.89 (0.98-6.01)	n.s.
WBC, mean, range	51.80 (0.6-348)	42.50 (0.5-400)	n.s.
Total blast count, mean, range	36.84 (1.3-344.5)	24.88 (0.1-364)	0.033
ANC, mean, range	6.925 (0.1–23.4)	6.137 (0.1-68.7)	n.s.
Platelets, mean, range	61.70 (7-455)	71.90 (5-451)	n.s.
PT, mean, range	81.20 (35-115)	77.30 (15-120)	n.s.
PTT, mean, range	28.1 (25-70)	30.4 (19-314)	n.s.
Fibrinogen, mean, range	395.80 (70-875)	343.10 (30-994)	0.01

WBC, ANC : $x10^3/\mu L$. RBC : $x10^6/\mu L$. Hb: g/dL. Platelets: $x10^3/\mu L$. Fibrinogen: mg/dL. Blood counts are at the onset of leukemia.

Table 2a. FAB types in AML.

FAB type	*Pneumonia*	*No pneumonia*
0	5 (45.5%)	6 (54.5%)
1	40 (40%)	60 (60%)
2	17 (21%)	64 (79%)
3	9 (16.7%)	45 (83.3%)
4	13 (20.6%)	50 (79.4%)
5	3 (15.8%)	16 (84.2%)
6	1 (14.3%)	6 (85.7%)
7	3 (37.5%)	5 (62.5%)

Table 2b. FAB types in ALL.

FAB type	*Pneumonia*	*No pneumonia*
1	6 (14.6%)	35 (85.4%)
2	11 (17.2%)	53 (82.8%)
3	1 (10%)	9 (90

p = n.s.

Table 3. Time from beginning of chemotherapy to onset of pneumonia according to outcome.

Days	*Positive*	*Death*
At diagnosis	15	11
< 7	17	6
7-14	12	7
14-21	9	9
> 21	14	9
Total	67	42

p= n.s.

Table 4. Etiology of pneumonias.

Aspergillus terreus	1
Aspergillus fumigatus	2
Aspergillus fumigatus + Staph. aureus	1
Staphylococcus aureus	4
Staphylococcus simulans	1
Staphylococcus epidermidis	2
Alpha-hemolyticus streptococcus	3
Enterococcus fecalis	2
Escherichia coli	3
Pseudomonas aeruginosa	3
Pseudomonas aeruginosa + Candida albicans	1
Stenotrophomonas maltophilia	2
Stenotrophomonas maltophilia + staphylococcus	1
Flavobacterium meningosepticum	2
Klebsiella pneumoniae	3

Among AML patients, 46 induction regimens contained idarubicin, and 45 daunorubicin; among ALL patients, 10 induction regimens contained idarubicin and 8 daunorubicin. At univariate analysis, advanced age, AML and total blast count significantly correlated with the risk of pneumonia. At multivariate analysis, only age ($p< 0.0001$) and total blast count ($p=0.002$) retained their prognostic significance. Fibrinogen levels at the time of diagnosis of leukemia were higher in the group of patients with pneumonia; even patients who developed pneumonia seven or more days after the beginning of chemotherapy had higher fibrinogen levels at the diagnosis of leukemia (385.26 mg/dL); this may reflect the presence of biochemical indices of infection before the chest X-ray became positive.

Twenty-six patients had pneumonia when chemotherapy for leukemia was begun. No significant correlation between outcome and the time interval from beginning of chemotherapy and onset of pneumonia could be shown.

Etiology

Most pneumonias were caused by bacteria: enteric aerobic Gram-negative, especially in the first years, Gram-positive (mostly *Staphylococci*) and less common Gram-negative species, such as *Stenotrophomonas maltophilia* and *Flavobacterium meningosepticum*.

A fungal etiology was microbiologically established in 4 cases when *Aspergillus* was isolated in BAL or lung biopsy; in 3 cases a diagnosis of *probable* fungal pneumonia was made according to a characteristic CAT picture (in one case *Aspergillus* was isolated in a nose culture). Table 4 shows causative micro-organisms, isolated either from blood cultures or from the lung (BAL or lung biopsy).

Outcome of pneumonia

Pneumonia responded to treatment in 67 patients, while 42 patients died. Among patients with pneumonia, 51 patients achieved a complete remission: 9/18 ALL and 42/91 AML.

As the outcome rate was the same in patients with AML and ALL, the analysis of prognostic factors for outcome of pneumonia was made on the whole group of patients.

In 11/42 patients the death was primarily attributed to a different cause (3 hemorrhage, 4 leukemia progression, 4 hemorrhage and leukemia progression).

Tables 5a and 5b detail the characteristics of patients divided according to the outcome: hematologic data are reported at the onset of leukemia, and at the onset, at day 7 and at the end of pneumonia.

At univariate analysis, the most significant determinant of a positive outcome was the achievement of complete remission. The following factors were also related to a positive outcome: a higher ANC, the absence of rales; a single infiltrate rather than multiple infiltrates or a diffuse pattern. The absence of microbiological

Table 5a. Characteristics of all patients with pneumonia according to outcome.

	Positive	*Death*	*p*
Patients	67	42	
Age in years mean (range)	54.3 (19-76)	57.4 (19-78)	n.s.
AML n, (%)	56 (61%)	35 (39%)	n.s.
ALL n, (%)	11 (61%)	7 (39%)	
Sex M n, (%)	32 (53%)	28 (47%)	0.04
Sex F n, (%)	35 (71%)	14 (29%)	
BDI n, (%)	15 (52%)	14 (48%)	n.s.
CDI n, (%)	52 (65%)	28 (35%)	
CR at the end n, (%)	47 (92%)	4 (8%)	< 0.0001
no CR at the end n, (%)	20 (34%)	38 (66%)	
Rales YES n, (%)	35 (51%)	34 (49%)	0.001
Rales NO n, (%)	32 (80%)	8 (20%)	
Pleural pain YES n, (%)	28 (62%)	17 (38%)	n.s.
Pleural pain NO n, (%)	39 (61%)	25 (39%)	
Single infiltrate n, (%)	31 (73%)	11 (27%)	0.003
Multiple infiltrates n, (%)	36 (54%)	31 (46%)	

Table 5b. Evolution of blood cell counts and fibrinogen levels.

	Positive	*Death*	*p*
Onset of AL			
Hemoglobin	8.59 (7.92-9.27)	8.76 (5.2-13.4)	n.s.
RBC	2.73 (2.52-2.96)	2.80 (1.36-5.97)	n.s.
WBC	54.4 (0.6-236)	47.6 (1-348)	n.s.
ANC	3.34 (0.1-12.5)	1.17 (0.3-23.4)	n.s.
Total blast count	38.3 (1.3-226.6)	34.3 (13.2-344.5)	n.s.
Platelets	73.5 (8-455)	56 (7-187)	n.s.
Fibrinogen	382 (70-875)	294 (153-820)	n.s.
Onset of pneumonia			
Hemoglobin	9.22 (6.4-15.8)	8.75 (5.5-13)	n.s.
WBC	18.7 (0.1-217))	15.3 (0.1-100)	n.s.
ANC	2.15 (0.1-17.32)	0.47 (0.3-2.33)	0.01
Platelets	28.3 (2-95)	19.2 (5-63)	n.s.
Fibrinogen	411.2 (122-654)	468.3 (149-990)	n.s.
Day 7 of pneumonia			
WBC	6.45 (1.31-31.7)	6.7 (1.43-13.7)	n.s.
ANC	3.54 (0-16.7)	0.68 (0.1-1.3)	0.001
End of pneumonia			
WBC	3.33 (0-14.9)	21.2 (0.1-288)	0.01
ANC	2.26 (0-9.5)	0.74 (0-7.5)	0.003

WBC, ANC: $x10^9$/L; RBC: $x10^6$/mL; Hb: g/dL; platelets: $x10^9$/L; fibrinogen: mg/dL. Abbreviations: AML: acute myelogenous leukemia; ALL: acute lymphoblastic leukemia; WBC: white blood cells; RBC: red blood cells; ANC: absolute neutrophil count; Hb: hemoglobin; BDI: bacteriologically demonstrated infections; CDI: clinically demonstrated infections; CR: complete remission; FAB: French-American-British classification.

demonstration of infection was also related to a good prognosis.

A multivariate analysis was performed including the parameters: hemoglobin, RBC, WBC, ANC, total blast count, platelets, fibrinogen, age, type of leukemia, sex, demonstration of infection, the presence of rales or pleural pain, single vs. multiple infiltrates. Only the achievement of complete remission and, with borderline significance, a single infiltrate maintained their prognostic value.

Two patients with fungal pneumonia had a CNS localization; they both died of their disease. In five patients, septic shock was the first manifestation of infection: 2 of them died (*Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia*) while three were cured (*Staphylococcus epidermidis, Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia*).

Discussion

Patients with acute leukemia who, because of age and good general condition, can be treated with intensive induction chemotherapy, now have significant rates of complete remission and long survival. Infectious complications are some of the most important hurdles to overcome before the achievement of remission.[9,10] Even though patients with advanced hematologic disease are at higher risk of developing pneumonia, the potential risk of death is particularly relevant in hematologic patients at diagnosis, when they can be potentially cured of their hematologic disease. For this reason we have included in our study only patients treated with regimens containing anthracyclines and have excluded patients treated with different regimens with palliative intent. No aggressive induction regimens without anthracyclines were employed in our institution in these years. Patients with acute leukemia evolved from known myelodysplastic syndromes or myeloproliferative disease and blast crises of CML were also excluded, because the risk of infections in these patients can be increased.

Among the factors related to the risk of pneumonia during induction therapy, age was the most significant, even though patients aged over 65 received reduced doses of chemotherapy. Leukemic mass, expressed as total blast count, was related to the risk of pneumonia. Both these factors maintained their prognostic significance also at multivariate analysis. The increased risk of pneumonia in AML patients, not maintained at multivariate analysis, was accounted for by increased age and total blood count in AML patients vs. ALL patients. Induction therapy for AML is associated with longer and more profound neutropenia and the risk associated with it may be higher than the risk associated with steroid therapy in ALL patients.

The identification of causative agents of pneumonia is often difficult because of the potential complications of invasive procedures in patients with low neutrophil and platelet counts. In particular, there may be more fungal pneumonias than those we can demonstrate with available techniques;[11,12] this has been shown by postmortem series.[13] For these reasons, criteria have been developed to allow diagnosis of *probable* or

possible fungal infections in neutropenic patients, even when a microbiological demonstration is not possible.[14] Discriminant scorecards have also been developed.[15] Although fungal pneumonias are more common in advanced phases of hematologic diseases, they can be present in patients at disease onset. In our group, a fungal etiology was microbiologically established in 4 cases, while in 3 cases it was considered as *probable*, based on radiologic criteria. Table 4 shows micro-organisms isolated both from the lung (BAL or lung biopsy) and from the blood. However, when a micro-organism is isolated from blood in a patient with pneumonia, it is not necessarily the cause of the pneumonia. Some of the factors associated with a poorer outcome can be evaluated at the onset of pneumonia: a lower ANC, the presence of rales and of multiple infiltrates.

When considering prognostic factors for outcome, it must be considered that it is generally difficult to distinguish between infectious and non-infectious causes of death in patients affected by a hematologic disease. Most infectious deaths occur in patients with unresponsive leukemia. As expected, neutropenia plays a crucial role in the evolution of pneumonia: this has been shown in various series.[16,17] At univariate analysis, achievement of complete remission, higher ANC, the absence of rales and a single infiltrate at the onset of pneumonia were associated with a positive outcome. Multivariate analysis confirms that the achievement of complete remission is far the most significant determinant of outcome; this is shown in most reported series.[2,17] Complete remission is associated with resolution of neutropenia and improvement of the underlying immune deficiency due to leukemia. Only 4/42 patients died after achievement of complete remission. Growth factors were used in most but not all patients starting from 1995 and their role in prevention or treatment of pneumonia cannot be evaluated in our group of patients. As different types of prophylaxis were used in different years, no conclusions can be drawn about the role of prophylaxis. Willhelm *et al.*,[17] analyzing 67 cases of pneumonia in 278 patients treated with induction therapy for AML, showed that pneumonia diagnosed within the 1st or 2nd week of chemotherapy had a lower response rate (43%) than the other pneumonias. In contrast, in our group of patients no significant correlation could be shown (Table 3) between the time interval from the beginning of the chemotherapy and onset of pneumonia and the outcome: patients who develop pneumonia later may be advantaged by a nearer rise of ANC; this can be balanced by the presence, among them, of patients whose prolonged neutropenia was a sign of failure to achieve complete remission. However a possible correlation may be difficult to show because nearly one quarter of our patients were diagnosed as having pneumonia before treatment began. Environmental or pharmacologic measures can be used to try to prevent pneumonia. The efficacy of drug prophylaxis, both antibacterial and antifungal, is controversial. Antifungal prophylaxis with non-absorbable drugs has not been shown to be effective in reducing systemic infections; fluconazole, the most widely used systemic prophylactic drug, is not effective against filamentous fungi, the most frequent cause of pulmonary fungal infections. The role of amphotericin, when used intravenously at low doses or as an aerosol or nasal spray, must still be supported by controlled studies. New perspectives can be opened by new azoles, such as itraconazole, especially when used as oral solution, or voriconazole.[18,19]

As previously mentioned, fungi may play an important role in these patients, so correct use of antifungal therapy appears critical to improving treatment of pneumonia in neutropenic patients. Amphotericin has been the most used antifungal parenteral drug. As its use, for the above reasons, is empirical in most cases, the most appropriate time to use it has not been clearly defined: in most institutions it is introduced after five or seven days of fever resistant to broad spectrum antibacterial therapy.[20] Earlier introduction in patients affected by pneumonia could be opportune, but the toxicity of conventional amphotericin B can be relevant, especially in patients receiving other nephrotoxic drugs (e.g. amikacin or cyclosporine). New lipid formulations of amphotericins are less toxic, even if more expensive; recent trials have shown their reduced toxicity as therapy of mycotic infections and as empiric therapy for neutropenic fever.[21] Trials are in progress to evaluate the optimal dose and the relative efficacy and toxicity of different preparations.[22]

However, the strong correlation shown by all groups between achievement of complete remission and response rate of pneumonia confirms that efforts to increase complete remission rates in acute leukemia are crucial for improving the outcome of pneumonia in these patients.

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FR: principal role in conception and design; analysis and interpretation, final approval of the version to be submitted. MV, PP, VS: analysis and interpretation, final approval of the version to be submitted. GG: analysis of data, concerning microbiological aspects. EMP, GC: critical revision for important intellectual content and final approval of the version to be submitted.

Disclosures

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Potential implications for clinical practice

- Defining risk of pneumonia in leukemia at onset, trying to identify high-risk groups. Analysis of factors associated with outcome.

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