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Dexamethasone in patients with acute lung injury from acute monocytic leukaemia

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ABSTRACT: The use of steroids is not required in myeloid malignancies and remains controversial in patients with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). We sought to evaluate dexamethasone in patients with ALI/ARDS caused by acute monocytic leukaemia (AML FAB-M5) *via* either leukostasis or leukaemic infiltration.

Dexamethasone (10 mg every 6 h until neutropenia) was added to chemotherapy and intensive care unit (ICU) management in 20 consecutive patients between 2005 and 2008, whose data were compared with those from 20 historical controls (1994–2002). ICU mortality was the primary criterion. We also compared respiratory deterioration rates, need for ventilation and nosocomial infections.

17 (85%) patients had hyperleukocytosis, 19 (95%) had leukaemic masses, and all 20 had severe pancytopenia. All patients presented with respiratory symptoms and pulmonary infiltrates prior to AML FAB-M5 diagnosis. Compared with historical controls, dexamethasone-treated patients had a significantly lower ICU mortality rate (20% *versus* 50%; p=0.04) and a trend for less respiratory deterioration (50% *versus* 80%; p=0.07). There were no significant increases in the rates of infections with dexamethasone.

In conclusion, in patients with ALI/ARDS related to AML FAB-M5, adding dexamethasone to conventional chemotherapy seemed effective and safe. These results warrant a controlled trial of dexamethasone *versus* placebo in AML FAB-M5 patients with noninfectious pulmonary infiltrates.

KEYWORDS: Acute lung injury, acute monocytic leukaemia, acute respiratory distress syndrome, dexamethasone, glucocorticoids

Among patients with acute leukaemia, up to half experience respiratory events early in the course of the disease [1, 2]. In this situation, progression to acute respiratory failure requiring ventilatory support is a severe complication that is not only frequently fatal [3, 4], but also delays the administration of optimal chemotherapy [5].

In patients with acute leukaemia and pulmonary infiltrates, infection must be sought and treated empirically [3]. However, pulmonary involvement may be directly due to the malignancy. In patients with myelomonocytic or monocytic acute leukaemia, leukaemia-related pulmonary involvement is frequent and severe [6–8]. The diagnosis rests on negative findings from extensive tests for the main infectious and noninfectious causes. Leukaemia-related pulmonary involvement includes pulmonary leukostasis, leukaemic pulmonary infiltrates and lysis pneumopathy [9–18]. We previously described 20 patients with acute monocytic leukaemia (AML; French–American–British (FAB) classification M5) who presented with either leukaemic infiltrates or leukostasis at the earliest phase of the malignancy [8]. All patients experienced lysis pneumopathy within hours of chemotherapy initiation. Mechanical ventilation and mortality rates were high, indicating a need to develop better treatment strategies. In addition to early intensive care unit (ICU) management, best supportive care, and rapid cytoreduction *via* hydration and chemotherapy, anti-inflammatory therapy would be expected to improve outcomes in these patients.

Steroid therapy has been used with variable results to prevent acute respiratory distress syndrome (ARDS) in high-risk patients [19], in short courses to treat early severe ARDS [20], and as rescue therapy in patients with persistent ARDS [21, 22]. In AML FAB-M5 patients, steroids would be expected to decrease cytokine and oxidant release, blast adhesion to endothelial cells and blast degeneration within the interstitium [15]. Steroids may both limit the extent of initial lung injury, as shown in patients with all-*trans*-retinoic acid (ATRA) syndrome [23], and prevent lysis pneumopathy.

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The objective of this study was to evaluate whether adding dexamethasone to the chemotherapy protocol in patients with AML FAB-M5 and acute lung injury (ALI)/ARDS due to leukaemic pulmonary involvement improved survival and decreased the incidence of respiratory deterioration and the need for ventilatory support.

PATIENTS AND METHODS

Consecutive patients with newly diagnosed and previously untreated AML FAB-M5 admitted to our ICU between January 1, 2005 and December 31, 2008 for acute respiratory failure were eligible for enrolment. The main inclusion criteria were as follows: 1) cytologically documented AML FAB-M5 (according to the World Health Organization classification, $\geqslant$20% leukaemic blasts in the bone marrow with monocytic cells comprising >80% of nonerythroids cells); 2) respiratory symptoms and pulmonary infiltrates at the earliest phase of AML FAB-M5; 3) ICU admission for acute respiratory failure defined by respiratory rate >30, oxygen saturation <90% or signs of respiratory distress; 4) no chemotherapy before ICU admission; and 5) no clinical or microbiological evidence of infection. Our institutional review board (Saint-Louis Teaching Hospital, Paris, France) approved the prospective data collection of AML cases, which was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonization, and Guidelines for Good Clinical Practice. The protocol for treating AML FAB-M5 patients with noninfectious pulmonary manifestations at the earliest phase of the disease was amended by the addition of dexamethasone. All patients were informed of the diagnosis of AML FAB-M5, the likelihood that the pulmonary manifestations were related to the leukaemia, and the use of dexamethasone added to conventional chemotherapy to limit the severity of ALI/ARDS severity and to prevent lysis pneumopathy.

ICU management was provided jointly by intensivists and haematologists. All patients underwent induction chemotherapy with an anthracycline plus cytarabine-based regimen. Based on previous experience in hyperleukocytic patients with acute promyelocytic leukaemia, dexamethasone has been preferred to methylprednisolone or hydrocortisone [24]. Dexamethasone (10 mg every 6 h *i.v.*) was given until leukopenia ($<1\ 1\times10^{9}\cdot L^{-1}$) occurred. ICU management included optimal ventilatory support with supplemental oxygen, noninvasive ventilation, and/or invasive mechanical ventilation as appropriate [25], and other life-sustaining therapies as required [8, 26]. All patients underwent noninvasive tests for pathogens in sputum, induced sputum, nasopharyngeal aspirates, blood and urine [25, 27]. Echocardiography was normal in all patients. Patients requiring endotracheal intubation routinely underwent bronchoscopy and bronchoalveolar lavage (BAL). Antibiotics covering community-acquired pathogens (third-generation cephalosporin or piperacillin-tazobactam plus a macrolide/quinolone) were given to all patients for 7 days, despite negative results for infection from all tests.

Variables listed in tables 1 and 2 were collected prospectively. Vital status at ICU and hospital discharge was known for all study patients.

Safety evaluation included mostly the proportion of patients presenting with hospital-acquired bacterial or opportunistic infection.

Statistical analysis

Quantitative parameters are reported as median (interquartile range; 25th–75th percentiles) and qualitative parameters as number and percentage. Comparisons were performed between the 20 patients given dexamethasone and 20 historical controls (previously published) who received the same treatment without steroids. ICU mortality was the primary evaluation criterion. Categorical variables were compared using the Chi-squared test or Fisher's exact test, as appropriate. Continuous variables were compared using the Mann–Whitney U-test or the Wilcoxon test, as appropriate.

Associations between patient characteristics and hospital mortality were assessed using a logistic regression model. Multivariable analysis was performed using stepwise forward selection to introduce variables whose p-values were <0.20 by univariate analysis. Then, the absence of a significant increase in the likelihood value after omission of each of the remaining variables was checked. Goodness of fit was evaluated using the Hosmer–Lemeshow statistic. Odds ratios and their 95% confidence intervals were computed. p-values <0.05 were considered statistically significant. Analyses were done using the SAS 9.1 software package (SAS Institute, Cary, NC, USA).

RESULTS

From January 2005 to December 2008, 450 patients with newly diagnosed acute myeloid leukaemia were admitted to the Saint-Louis Teaching Hospital, including 45 (10%) with AML FAB-M5, of whom 20 (44%) required ICU admission before chemotherapy initiation for respiratory manifestations with onset before the diagnosis of leukaemia (fig. 1). Of these 20 patients, 11 were admitted directly to the ICU for acute respiratory failure and nine were transferred from the haematological wards within 12 (6–36) h of admission. In 14 patients, AML FAB-M5 was diagnosed during the ICU stay.

As reported in table 1, there were 13 males and seven females with a median age of 42 (33–60) yrs. None had any comorbidity. All patients had severe acute respiratory failure with tachypnoea and profound hypoxaemia. The chest radiographs consistently showed diffuse lung infiltrates. The Simplified Acute Physiology Score version II score was 39 (29–50). All 20 patients were febrile and all but one had physical evidence of leukaemic masses. Laboratory findings included high white blood cell count in 17 patients, circulating blast cells in 16 and platelet count $<50\ 1\times10^{9}$ cells$\cdot L^{-1}$ in 12. The three patients without hyperleukocytosis had $<10\ 1\times10^{9}$ cells$\cdot L^{-1}$ with no circulating blast cells. Disseminated intravascular coagulation was present in seven patients.

As shown in table 2, within a few hours after chemotherapy initiation, 10 patients had no respiratory status deterioration or increase in oxygen requirements and 10 had a deterioration in oxygenation requiring invasive mechanical ventilation. An additional patient required intubation and ventilation because of complex ventricular arrhythmia. Median length of ICU stay was 7 days (3.5–14). ICU and hospital survival rates were both 80% (four deaths). All 16 survivors were in remission after neutropenia recovery and received consolidation chemotherapy, and 1-yr survival was 60% (eight deaths).

None of the baseline characteristics differed significantly between the historical controls and the dexamethasone-treated

TABLE 1 Patient characteristics at intensive care unit (ICU) admission

Characteristic	Historical controls	Dexamethasone group	p-value
Subjects n	20	20	
Demographics			
Age yrs	50 (36–65)	42 (33–60)	0.38
Male	13 (65)	13 (65)	0.99
Respiratory symptoms at presentation			
Respiratory rate breaths·min^{-1}	33 (29–40)	31 (22–36)	0.11
Diffuse crackles at lung auscultation	11 (55)	10 (50)	0.88
P_{a,O_2} on room air at admission mmHg	44 (38–53)	44 (37–57)	0.67
Lower S_{p,O_2} on room air %	80 (55–92)	77 (60–95)	0.44
Time from dyspnoea onset days	2 (1–5)	3 (0–19)	0.50
Clinical presentation of AML FAB-M5 at ICU admission			
Headaches	4 (20)	4 (20)	0.99
Tonsil infiltration	7 (35)	6 (30)	0.45
Spleen and liver enlargement	14 (70)	17 (85)	0.14
Gingival infiltration	10 (50)	10 (50)	0.99
DIC	4 (20)	14 (70)	0.003
Temperature °C	38.4 (37.7–39.0)	38.7 (37.7–39.5)	0.66
Leukocyte count 1×10^9 cells·L^{-1}	98 (15–183)	149 (100–204)	0.08
Circulating blast cell count 1×10^9 cells·L^{-1}	100 (65–169)	106 (83–180)	0.87
Platelet count 1×10^9 cells·L^{-1}	32 (19–68)	52 (32–70)	0.20
Haemoglobin level g·dL^{-1}	9.2 (7.2–19)	8.9 (7.1–9.8)	0.48
Radiographic findings			0.14
Bilateral alveolar opacities	14 (60)	7 (35)	
Bilateral interstitial opacities	5 (25)	10 (50)	
Focal opacity	1 (5)	3 (15)	
Pleural effusion	3 (15)	5 (25)	

Data are presented as median (interquartile range) or n (%), unless otherwise stated. P_{a,O_2}: partial pressure of oxygen in arterial blood; S_{p,O_2}: arterial oxygen saturation measured by pulse oximetry; AML FAB-M5: acute monocytic leukaemia French–American–British subtype 5; DIC: diffuse intravascular coagulation.

TABLE 2 Intensive care unit (ICU) management in historical control patients and in patients given dexamethasone

	Historical controls	Dexamethasone group	p-value
Subjects n	20	20	
SAPS II at ICU admission	44 (35–51)	39 (29–50)	0.54
Time from hospital to ICU admission days	1 (0–3)	0.5 (0–3)	0.85
Bronchoscopy and BAL performed	20 (100)	5 (20)	0.01
Deterioration of respiratory status after chemotherapy initiation			
None	0 (0)	4 (20)	0.07
Increased oxygen needs	4 (20)	6 (30)	
Invasive mechanical ventilation	15 (75)	10 (50)	
Use of NIV	11 (55)	3 (15)	0.01
Need for NIV or invasive MV	15 (75)	11 (55)	0.18
Cardiac arrest after chemotherapy initiation	3 (15)	1 (5)	0.29
ICU-acquired events			
Invasive fungal infection	3 (15)	1 (5)	0.37
Hospital-acquired infection	7 (35)	2 (10)	0.05
Septic shock	11 (55)	6 (30)	0.10
Length of ICU stay days	8 (3.5–18.5)	7 (3.5–14)	0.67
ICU mortality	10 (50)	4 (20)	0.04

Data are presented as median (interquartile range) or n (%), unless otherwise stated. SAPS II: Simplified Acute Physiology Score version II; BAL: bronchoalveolar lavage; NIV: noninvasive mechanical ventilation; MV: mechanical ventilation.

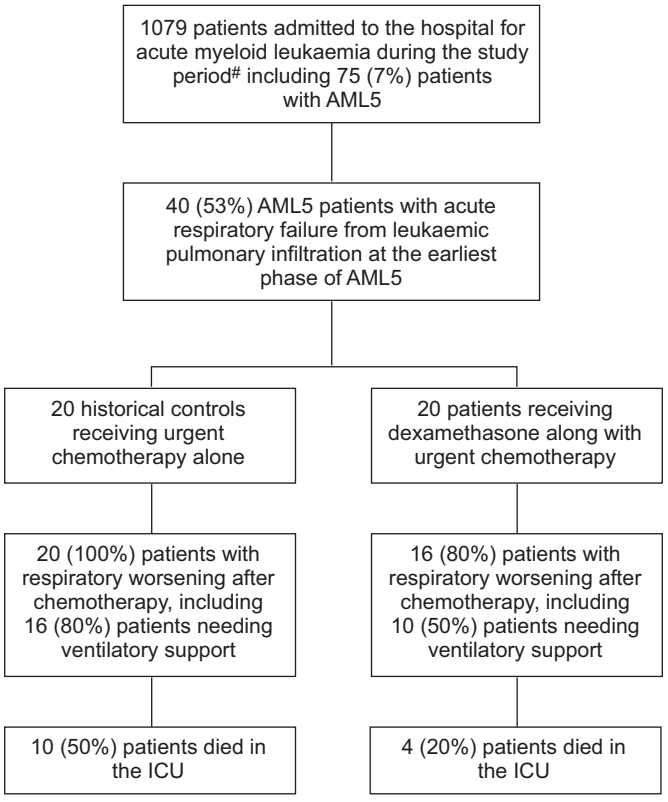

FIGURE 1. Patient flow chart. ICU: intensive care unit; AML5: acute myelocytic leukaemia FAB-M5. #: the study periods ran from January 1994 to July 2002 and from January 2005 to December 2008.

patients (tables 1 and 2). In particular, the severity of respiratory failure and characteristics of the leukaemia were well balanced between the two groups.

In-ICU mortality was significantly lower in the dexamethasone group than in the control group (20% *versus* 50%; p=0.04). In the dexamethasone-treated group, we found decreases in the occurrence of respiratory status deterioration, need for increased oxygen flow and need for ventilatory support compared with the controls (fig. 2). Chemotherapy initiation was followed by respiratory status deterioration in only four (20%) dexamethasone-treated patients compared with 20 (100%) controls.

Dexamethasone therapy was not associated with increased rates of hospital-acquired bacterial or invasive fungal infections.

Table 3 reports the results of the multivariate analysis for factors associated with ICU mortality. Higher respiratory rate and lower arterial oxygen saturation measured by pulse oximetry at ICU admission were independently associated with ICU mortality. Dexamethasone therapy was associated with a trend for a decrease in ICU mortality by multivariate analysis.

DISCUSSION

We evaluated the efficacy and safety of dexamethasone therapy in patients with AML FAB-M5 and noninfectious pulmonary infiltrates. Compared with historical controls who did not receive dexamethasone, patients given dexamethasone had a decrease in the severity of pulmonary involvement and a lower rate of respiratory status deterioration after chemotherapy

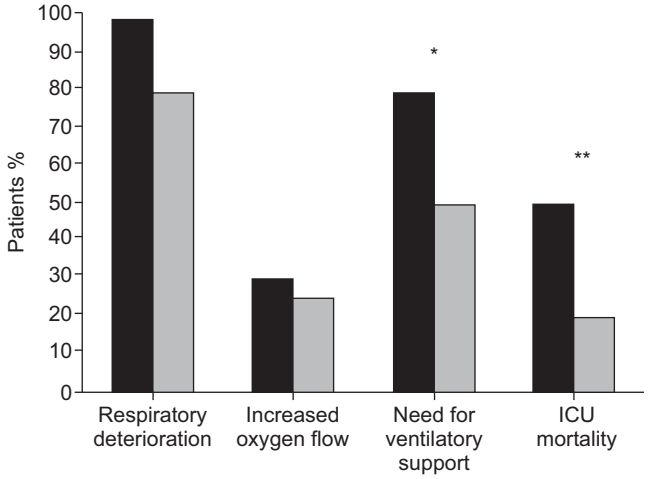

FIGURE 2. Impact of dexamethasone therapy on clinical outcomes. An additional patient from the dexamethasone group received ventilation for complex arrhythmia. ■: dexamethasone-treated patients; ■: historical controls. ICU: intensive care unit. *: p<0.05; **: p<0.01.

initiation. ICU mortality was lower in the dexamethasone-treated patients than in the historical controls.

Pulmonary leukostasis occurs in patients with acute myeloid leukaemia and rapidly increasing white blood cell count [10, 11], and is consistently present when the count exceeds 200 1×10^9 cells·L^{-1} [12]. Pulmonary leukostasis leads to endothelial injury and activation from microvascular invasion, with hyperviscosity, leukocytic microthrombi, oxygen steal and hypoxia [13–15]. Leukaemic pulmonary infiltrates occur in patients with or without hyperleukocytosis. This fact suggests that both the type of the blasts and their affinity for the pulmonary endothelium may be responsible for lung injury [8, 28]. Autopsy studies have shown blast aggregates within the vessel lumina [29]. The infiltrates typically follow the lymphatic routes along the bronchovascular bundles, interlobular septa and pleural interstitial tissue [16–18]. Finally, lysis pneumopathy occurs either immediately or early after chemotherapy initiation as a manifestation of acute tumour lysis syndrome. Lysis pneumopathy results in diffuse alveolar damage [30] and is most common in

TABLE 3 Factors independently associated with intensive care unit (ICU) mortality by multivariable analysis

	Odds ratio	95% confidence interval	p-value
Respiratory rate at admission per point	1.22	1.01–1.48	0.036
Dexamethasone (*versus* historical controls)	0.12	0.01–1.23	0.054
Time from hospital to ICU admission per day	1.17	0.97–1.40	0.098
SAPS II score at ICU admission per point	1.06	0.96–1.17	0.216

SAPS II: Simplified Acute Physiology Score version II.

patients with hyperleukocytic acute myeloid leukaemia, particularly the myelomonocytic subtypes with abnormal marrow eosinophils [31].

Steroids have been used in early severe ARDS to improve oxygenation by decreasing lung collagen and oedema formation [32, 33]. However, steroid use in patients with persistent ARDS is controversial [21, 22]. Steroids are a major component of the treatment regimen for acute lymphocytic leukaemia but are not used in patients with acute myeloid leukaemia [34]. In patients with promyelocytic leukaemia given ATRA, dexamethasone was very effective in preventing or treating ATRA-related pulmonary toxicity [23, 35].

Noninfectious pulmonary involvement is particularly common in patients with hyperleukocytotic myeloid leukaemia, particularly of the M4 and M5 subtypes [18]. In a previous study, we described 20 AML FAB-M5 patients with acute respiratory failure from pulmonary leukostasis and leukaemic infiltration before the diagnosis of leukaemia [8]. All 20 patients had post-chemotherapy lysis pneumopathy. 10 patients died, indicating a need for an intervention targeting the pathophysiological mechanisms responsible for the initial lung injury and subsequent respiratory status deterioration. Steroid therapy was a good candidate, as steroids are widely used in various subsets of ALI [33] and chemotherapy-related pulmonary toxicity [23]. Our data suggest that steroid therapy may not only limit pulmonary leukostasis and leukaemic infiltration, but also prevent lysis pneumopathy. Compared with the control group, the dexamethasone-treated group was characterised by lower rates of respiratory status deterioration, mechanical ventilation and death. We found no significant increase in infections in the dexamethasone-treated group compared with the control group.

Our study has several limitations. We used historical controls, and the recruitment period from the first control to the last dexamethasone-treated patient spans 15 yrs, during which time changes in the management of ALI/ARDS and increasing experience may have affected patient outcomes [36]. However, the dexamethasone and control patients were not different at baseline and received the same haematological and ICU management. Our data suggest that a multicentre randomised controlled trial testing the risk/benefit ratio of dexamethasone in patients with AML FAB-M5 and noninfectious pulmonary involvement may be warranted. Whether such a trial should be extended to all patients with acute leukaemia-related noninfectious pulmonary involvement requires discussion. A second limitation of the study is that we did not record noninfectious adverse effects of dexamethasone therapy (*e.g.* poor glucose control). Future studies will need to record all possible adverse effects. Last, we assumed that all patients with AML FAB-M5, acute respiratory failure, pulmonary infiltrates and negative tests for infection had leukaemia-related pulmonary involvement. This reflects our standard diagnostic strategy, which is supported by five arguments. First, *post mortem* studies have established that the noninfectious pulmonary complications of acute leukaemia include leukostasis, leukaemic infiltration and lysis pneumopathy [8], as well as alveolar proteinosis, which is extremely rare [37]. Secondly, opportunistic infections are not encountered at the earliest phase of AML [3]. In contrast to patients with acute lymphoid leukaemia, patients with AML FAB-M5 and infection usually have community-acquired bacteria. All our patients received combination antibiotic therapy for 7 days starting at ICU admission. However, we cannot strictly rule out the diagnosis of infection, based on our data including *post mortem* biopsies in only two historical controls. Along this line, CONFALONIERI *et al*. [38] reported benefits from steroids in patients with severe community-acquired pneumonia. Thirdly, our study was done in a homogeneous group of patients with AML FAB-M5 patients (monocytic subtype) and inaugural respiratory failure. Among the 20 historical controls, diffuse haemorrhage by BAL and *post mortem* biopsies was a major finding. We believe this finding is sufficiently suggestive to maintain a high level of suspicion for leukaemia-related pulmonary infiltrates in patients with untreated AML FAB-M5 and inaugural acute respiratory failure. However, overlap may occur between lysis pneumopathy and cytarabine-induced pulmonary toxicity. Such overlap would further support steroid therapy [39]. Fourthly, all patients underwent noninvasive diagnostic tests to rule out infection [25, 27]. Also, all intubated patients underwent bronchoscopy and BAL, which consistently showed diffuse alveolar haemorrhage. Fifthly, the decrease in ICU mortality among dexamethasone patients in our study supports our presumptive diagnosis of leukaemia-related pulmonary involvement without infection. Lastly, changes in mortality between historical controls and steroid-treated cases could have been ascribable to differences in ICU management and ventilatory strategies. However, median tidal volume was 9 (6–10) $mL \cdot kg^{-1}$ in historical controls and 9 (7–10) $mL \cdot kg^{-1}$ in steroid-treated cases (p-value not significant). Corresponding figures for positive end-expiratory pressure were 7 (2–11) and 9 (5–15) cmH_2O (p-value not significant).

In summary, adding dexamethasone to the chemotherapy regimen in AML FAB-M5 patients with acute respiratory failure from leukaemia-related pulmonary involvement significantly diminished ICU mortality. In addition, the rate of post-chemotherapy deterioration and the need for ventilatory support decreased with dexamethasone therapy. These results suggest that dexamethasone may be effective in decreasing leukaemic pulmonary infiltration and leukostasis and in preventing lysis pneumopathy. We found no increase in infection rates with dexamethasone therapy. Although these data are not sufficient to make a recommendation about using dexamethasone, they warrant a trial of dexamethasone in patients with AML FAB-M5 presenting as acute respiratory failure without evidence of infection.

SUPPORT STATEMENT

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STATEMENT OF INTEREST

None declared.

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