Worsening of Respiratory Status during Neutropenia Recovery in Noncritically Ill Hematological Patients: Results of a Prospective Multicenter Study

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Key Words

Acute respiratory failure · Malignancy · Pulmonary infection

Abstract

Background: Neutropenia recovery (NR) has been associated with worsening preexisting lung injury in up to 50% of critically ill cancer patients. However, only limited relevant data exist in the general population of hematological patients. **Objectives:** To assess the incidence of acute respiratory deterioration during NR in patients with hematological malignancies. **Methods:** Adult patients with neutropenia expected to last more than 7 days were included. Worsening of respiratory status (WRS) was defined as a decrease in oxygen saturation of $\geq 5\%$, the need for oxygen therapy for ≥ 24 h, an increase in oxygen flow of $\geq 50\%$ in patients previously treated with oxygen, or the need for mechanical ventilation. NR was defined as the 3 days preceding or following a neutrophil count of $>0.5 \times 10^9/l$. **Results:** A total of 16 of 50 patients included in this pilot study experienced WRS during NR (32%), and 13 patients had WRS during neutropenia (26%). The incidence density of WRS was $0.53 (\pm 0.79)$ episodes per

10 days during NR and $0.20 (\pm 0.39)$ episodes per 10 days during neutropenia ($p = 0.004$). Sepsis, stem cell transplantation, preexisting pneumonia, or the use of granulocyte colony-stimulating factor were not associated with WRS during NR. **Conclusion:** Up to one third of noncritically ill hematological patients with expected neutropenia of more than 7 days experience WRS during NR. Clinical consequences and risk factors for WRS during NR remain to be evaluated.

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Introduction

Acute respiratory failure remains the main reason for admission of cancer patients to the intensive care unit (ICU) and is associated with a high morbidity and mortality [1, 2]. A total of 5–12% of patients with hematological malignancies require ICU admission as a result of acute respiratory failure, and hospital mortality has been reported to be as high as 50% [2].

In patients with chemotherapy-induced neutropenia, acute respiratory failure is often the result of several in-

teracting factors including pulmonary infection, cardiogenic pulmonary edema, alveolar hemorrhage, and direct toxicity of anticancer agents [3–7]. In addition, the use of granulocyte colony-stimulating factor (G-CSF) has been associated with a deterioration of respiratory status [3–7]. Neutropenia recovery (NR) is a risk factor for the deterioration of respiratory status or exacerbation of preexisting lung injury [8–10], and this deterioration usually occurs during the 3 days flanking NR [2, 9, 11, 12]. Preexisting pulmonary infection [9], prolonged aplasia [9], and rapid NR [10] have been reported as risk factors for the deterioration of respiratory status during NR. Up to 50% of critically ill patients experience a deterioration of their respiratory status during NR [9, 11, 12], but little information is available for less severe hematological patients (i.e. neutropenic patients who did not require ICU admission) [8, 10, 13]. NR has been reported to be associated with the deterioration of oxygenation and changes in lung microvascular permeability [8]; however, the small number of reported cases outside of the ICU, the lack of adequate evaluation of the incidence density of respiratory deterioration during NR, and the lack of comparison with acute respiratory failure during neutropenia has left a need for additional studies in this patient population.

The primary objective of this prospective study was to assess the incidence and incidence density of worsening of respiratory status (WRS) during neutropenia and NR in hematological patients. The secondary objective was to assess the influence of the usual risk factors of WRS during NR.

Patients and Methods

Patients

We performed a prospective multicenter cohort study of non-consecutive patients admitted to three hematology units located in two university hospitals (Saint-Louis University Hospital, Paris, France, and Lucien Neuwirth Cancer Institute of the Loire, Saint-Priest-En-Jarez, France). This study took place from January 2012 to August 2013 and was approved by the Institutional Review Board of the Société de Réanimation en Langue Française (CE SRLF 11-338). According to French law, the need for written informed consent was waived, but patients were informed of the study, and none refused to participate.

Adult patients (≥ 18 years old) with underlying hematological malignancies were included if they met the following criteria: being admitted to one of the participating hematology units; needing cancer chemotherapy or hematopoietic stem cell chemotherapy conditioning, and having an expected chemotherapy-induced neutropenia duration of ≥ 7 days. Patients were included in the study the day before the start of cancer chemotherapy. In cases of multiple hospitalizations, patients already included in the study were included only once. Patients with hematological malignancies in the ICU were not included.

Data Collection and Definitions

Patient characteristics, characteristics of the underlying hematological malignancy, and type of cancer chemotherapy were collected from patient charts at study inclusion. Temperature, respiratory characteristics, peripheral oxygen saturation (SpO_2), clinically or microbiologically documented infection, white blood cell count, and G-CSF use were collected during hospitalization. Finally, episodes of deterioration of respiratory status and clinical, microbiological, and radiological characteristics were collected.

WRS was defined as a decrease in SpO_2 of $\geq 5\%$ when compared to baseline, the need for oxygen therapy for >24 h, the need to increase oxygen flow by $>50\%$ in patients previously treated with oxygen, or the need for invasive or noninvasive mechanical ventilation. Neutropenia was defined as a neutrophil count $<0.5 \times 10^9/\text{l}$. NR was defined as the period of 3 days preceding and following the first day with an absolute neutrophil count of $\geq 0.5 \times 10^9/\text{l}$.

Statistical Analysis

Results are reported as medians (interquartile range, IQR) or numbers and percentages. Comparisons between groups were performed using nonparametric tests (Fisher's exact test, Mann-Whitney U test, and Wilcoxon test) as appropriate. In order to evaluate the influence of NR on respiratory status, the crude incidence (number of episodes during neutropenia and during NR) and the incidence density (number of episodes per 10 days of neutropenia or NR) were planned a priori to be reported.

Finally, we performed logistic regression analyses to identify variables that were significantly associated with WRS during NR, as assessed by estimating odds ratios (ORs) and their 95% confidence intervals (95% CIs). Variables yielding p values <0.25 in the bivariate analyses were entered into a forward stepwise logistic regression model where respiratory status worsening during NR was the outcome variable of interest. The covariates were removed from the model with critical removal of p values of 0.1. Log-linearity of continuous variables was verified, as was the correlation between the selected variables. All tests were two-sided, and p values <0.05 were considered statistically significant. All statistical analyses were performed using SPSS 13.0 software.

Results

Patients' Characteristics

Fifty patients with hematologic malignancies were included, and their main characteristics are reported in table 1. Thirty-one patients (62%) were male, and the median age of the patient group was 56 years (IQR 39–65). The underlying malignancy was acute leukemia in 33 patients (66%), multiple myeloma in 8 (16%), lymphoma in 8 (16%), and myelodysplastic syndrome in 1 patient (2%). Of the 50 included patients, 24 underwent stem cell transplantation induction (including induction of allogeneic stem cell transplantation in 9 patients and autologous stem cell transplantation in 15 patients), 16 had induction chemotherapy, and 10 had consolidation chemotherapy.

Table 1. Patients' main characteristics

	All patients (n = 50)	WRS during NR (n = 16)	No WRS during NR (n = 34)	p value
Male gender	31 (62)	9 (56)	22 (64)	0.75
Age, years	56 (39–65)	63 (55–69)	50 (35–60)	0.03
<i>Underlying hematological malignancy</i>				
Acute leukemia	33 (66)	9 (56)	24 (71)	0.35
Hodgkin's lymphoma	4 (8)	2 (13)	2 (6)	0.58
Non-Hodgkin's lymphoma	4 (8)	4 (25)	0	0.008
Myeloma	8 (16)	0	8 (24)	0.04
Myelodysplastic syndrome	1 (2)	1 (6)	0	0.32
<i>Treatment delivered</i>				
Allogeneic stem cell transplantation	9 (18)	3 (19)	6 (47)	0.99
Autologous stem cell transplantation	15 (30)	5 (31)	10 (30)	1.00
Induction course	16 (32)	4 (25)	12 (35)	0.53
<i>Chest X-rays at admission</i>				
Normal	46 (92)	16 (100)	30 (88)	0.16
Alveolar	1 (2)	0	1 (3)	1.00
Interstitial	3 (6)	0	3 (9)	0.54
Neutropenia duration, days	16 (10–21)	14 (11–20)	17 (9–21)	0.87
<i>During neutropenia</i>				
Fever	46 (92)	14 (88)	32 (94)	0.58
Clinical documentation	7 (15)	3 (21)	4 (13)	0.66
Microbiological documentation	16 (35)	7 (50)	9 (28)	0.33
Pneumonia	5 (10)	3 (19)	2 (6)	0.14
Probable invasive fungal infection	2 (4)	1 (6)	1 (3)	0.54
WRS during neutropenia ^a	13 (26)	5 (31) ^a	8 (24)	0.73
G-CSF administration	41 (82)	14 (88)	27 (80)	0.70
Hospital length of stay, days	29 (22–38)	29 (24–40)	29 (20–38)	0.80

Values are presented as n (%) or median (IQR).

^a Including a single patient with 2 episodes of WRS during neutropenia.

At study inclusion, most of the patients had a normal chest X-ray (n = 46; 92%), 3 patients had bilateral interstitial infiltration, and 1 patient had alveolar condensation. The median respiratory rate was 16 (IQR 16–20), and the median SpO₂ was 98% (IQR 96–99). The median length of hospital stay was 29 days (22–38).

Neutropenia

The median duration of neutropenia was 16 days (IQR 10–21). Fever was observed during neutropenia in the majority of the patients (n = 46; 92%): 23 patients (46%) had fever of unknown origin, and 23 patients (46%) had a clinically or microbiologically documented infection. Five patients experienced clinically or microbiologically docu-

mented pneumonia (10%), and 2 patients (4%) developed a probable invasive fungal infection. Most of the patients received prophylactic G-CSF during neutropenia (82%).

Worsening of Respiratory Status

Overall, 24 of the included patients (48%) met the criteria for WRS, including 13 patients with episodes of WRS during neutropenia (26%) and 16 patients with WRS during NR (32%) (p = 0.30). Five patients had 2 episodes of WRS (1 transient episode during neutropenia and 1 episode during NR). A single patient experienced 2 episodes of WRS during neutropenia. The incidence density of WRS was 0.20 (±0.39) per 10 days of neutropenia and 0.53 (±0.79) per 10 days of NR (p = 0.004; fig. 1).

Fig. 1. WRS incidence density per 10 days of neutropenia and per 10 days of NR ($p = 0.004$). Error bars represent 95% CI.

Fig. 2. Mean SpO₂ at baseline, 3 days before NR (D-3), the day of NR (D0) and 3 days after NR (D+3) in patients with and without WRS. Error bars represent 95% CI.

Risk Factors of WRS during NR

The main factors associated with WRS during NR are reported in table 1. Before adjustment, WRS was more frequent in patients with non-Hodgkin's lymphoma ($n = 4$; 25%), and no patient with myeloma experienced this complication. Stem cell transplantation, clinically or microbiologically documented infection, history of pneumonia during neutropenia, suspicion of aspergillosis, and G-CSF use were not associated with WRS during NR.

After adjustment for confounders, only two variables were retained in the final logistic regression model as associated with WRS during NR: preexisting altered respiratory status as assessed by SpO₂ at study inclusion (OR 0.50 per point; 95% CI 0.27–0.91) and occurrence of WRS during neutropenia (OR 25.4; 95% CI 0.90–711) (Hosmer-Lemeshow goodness-of-fit test: $p = 0.35$; C-stat = 0.92).

SpO₂ was lower on the third day preceding NR in patients with WRS during NR [SpO₂ 94% (IQR 92–95) vs. 96% (IQR 95–98) in patients without WRS; $p = 0.002$; fig. 2]. A single patient required ICU admission as a consequence of respiratory failure during NR and died before discharge.

Discussion

To the best of our knowledge, this is the first study to assess the risk of WRS during NR in hematological patients who did not require ICU care. Our study has yielded three important findings. First, our results confirm the risk of WRS during NR even in the absence of severe pre-existing pulmonary injury. Second, WRS occurrence is frequent, and up to one third of patients with hematological malignancies and neutropenia of ≥ 7 days' duration experience WRS during NR. Third, the results suggest that lower arterial saturation at chemotherapy initiation and WRS during neutropenia might be risk factors for WRS during NR.

NR was described three decades ago as increasing the risk of deterioration of oxygenation and abnormal lung microvascular permeability [8]. Since that time, others have reported similar findings [9, 10, 12–14], including several studies that have assessed risk of WRS in critically ill patients [9, 12, 14]. For example, up to half of critically ill cancer patients with NR experience WRS [1, 12]. Information about noncritically ill patients is scarce, however, and relies mainly on small case series [8, 10, 13]. Of interest, WRS has been associated with increased lung microvascular permeability in one of the reported patients [8]. Moreover, Demuynck et al. [13] emphasized that preexisting lung injury or severe infection was observed in each of their patients. Our study suggests that up to one third of hematology patients with an expected neutropenia duration of more than 7 days experience this event.

Previous investigations did not assess the exact influence of NR on deterioration of respiratory status. Hence, the deterioration of respiratory status during NR might be related to an increased risk during this period or to a fortuitous association between these two events. In the

same way, WRS during NR may be related to pulmonary infection at the time of NR. Todeschini et al. [10] assessed the risk of respiratory events following NR in patients with pulmonary aspergillosis. Of the 20 patients included in their study, 40% experienced a pulmonary event. Moreover, these respiratory events were independently associated with neutrophil count 5 days after NR, suggesting that the rapid increase in neutrophil count might be a risk factor for a respiratory event in patients with aspergillosis [10]. In our study, both WRS and rate of worsening were greater during NR than during neutropenia (0.53 ± 0.79 events per 10 days of NR compared to 0.20 ± 0.39 events per 10 days of neutropenia; $p = 0.004$). This finding further indicates that NR might be a specific risk factor for respiratory worsening.

Several risk factors for WRS have been noted in previous studies. These include longer neutropenia duration [9], preexisting respiratory failure or infection [8, 12, 13, 15], the need for mechanical ventilation [12], and G-CSF use [11, 13, 16]. Nevertheless, the pathophysiology of WRS remains debated. In patients with acute respiratory distress syndrome (ARDS) during NR, alveolar macrophages are the predominant cells in broncho-alveolar lavage [9]. These alveolar macrophages are thought to contribute to the development of ARDS, probably by producing proinflammatory cytokines such as tumor necrosis factor and interleukin-1 that increase alveolar permeability [9]. Additionally, lung neutrophil recruitment and activation might trigger respiratory failure, especially in patients with preexisting lung injury. Hence, immature neutrophils released from bone marrow during NR might accumulate in lung microvessels [17]. Results from experimental studies have suggested that pulmonary injury caused by cigarette smoking is associated with a sequestration of younger neutrophils released from the bone marrow within pulmonary microvessels, thus contributing to the alveolar capillary wall damage seen in ARDS [18]. In addition, infection shortens the transit time of neutrophils in the marrow, possibly resulting in the release into the peripheral blood of immature neutrophils containing higher levels of lysosomal enzymes that may ultimately be more likely to be sequestered in the lung vessels and contribute to ARDS [19]. In the present study, preexisting lung injury was the main factor associated with WRS.

Our study has several limitations. First, the preliminary design led to a limited sample size and, therefore, to a lack of statistical power. Second, although we reported a high prevalence of WRS during NR and that NR was associated with a higher rate of events compared to neutropenia, assessment of risk factors for this event was lim-

ited. Thus, an absence of influence of neutropenia duration, aspergillosis, or G-CSF might reflect the limited impact of these variables on the event of interest, the lack of statistical power, our inability to demonstrate their influence, or a combination of these factors. Third, mortality was low in our study population, and only 1 patient experienced a severe respiratory failure requiring ICU admission. Thus, the clinical relevance of our findings is debatable. As a consequence, additional and larger studies are required to more clearly assess the risk factors and clinical consequences of WRS during NR in hematology ward patients. Last, SIRS or sepsis criteria at the time of WRS were not recorded, and this association was not evaluated by previous studies in this field. Therefore, the association of WRS during NR with SIRS criteria remains largely unknown. Future studies may need to record these variables in order to clarify the clinical presentation of this pulmonary event and to suggest a hypothesis with regard to its physiopathology.

This preliminary study confirms that NR is associated with WRS in hematological patients. Additionally, the results underline the high incidence of this event, confirm that NR is associated with an increased rate of WRS when compared to neutropenia, and suggest that preexisting lung dysfunction is the main risk factor for WRS. Regarding our findings, additional research with a larger population is warranted to confirm these results, detect risk factors, and assess the long- and short-term clinical consequences of these events for patients.

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