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

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10 days during NR and 0.20 (±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-
interacting factors including pulmonary infection, cardio-
genic 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 dete-
rmination of respiratory status or exacerbation of preexist-
ing lung injury [8–10], and this deterioration usually oc-
curs during the 3 days flanking NR [2, 9, 11, 12]. Preexist-
ing 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 infor-
mation is available for less severe hematological patients
(i.e. neutropenic patients who did not require ICU admis-
sion) [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 respira-
tory 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 in-
formed 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: be-
ing 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 malignan-
cies in the ICU were not included.

Data Collection and Definitions

Patient characteristics, characteristics of the underlying hema-
tological malignancy, and type of cancer chemotherapy were col-
lected from patient charts at study inclusion. Temperature, respira-
tory characteristics, peripheral oxygen saturation (SpO₂), clin-
ically or microbiologically documented infection, white blood cell
count, and G-CSF use were collected during hospitalization. Fi-
nally, episodes of deterioration of respiratory status and clinical,
microbiological, and radiological characteristics were collected.

WRS was defined as a decrease in SpO₂ of ≥5% when compared
to baseline, the need for oxygen therapy for >24 h, the need to in-
crease oxygen flow by >50% in patients previously treated with
oxygen, or the need for invasive or noninvasive mechanical venti-
lation. Neutropenia was defined as a neutrophil count <0.5 × 10⁹/l.
NR was defined as the period of 3 days preceding and following the
first day with an absolute neutrophil count of ≥0.5 × 10⁹/l.

Statistical Analysis

Results are reported as medians (interquartile range, IQR) or
numbers and percentages. Comparisons between groups were per-
formed 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 inci-
dence (number of episodes during neutropenia and during NR)
and the incidence density (number of episodes per 10 days of neu-
tropenia 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% confi-
dence intervals (95% CIs). Variables yielding p values <0.25 in the
bivariate analyses were entered into a forward stepwise logistic re-
gression 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-linear-
ity of continuous variables was verified, as was the correlation be-
tween the selected variables. All tests were two-sided, and p values
<0.05 were considered statistically significant. All statistical anal-
yses were performed using SPSS 13.0 software.

Results

Patients’ Characteristics

Fifty patients with hematologic malignancies were in-
cluded, and their main characteristics are reported in ta-
ble 1. Thirty-one patients (62%) were male, and the me-
dian age of the patient group was 56 years (IQR 39–65).
The underlying malignancy was acute leukemia in 33 pa-
tients (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 allo-
geneic stem cell transplantation in 9 patients and autol-
ogous stem cell transplantation in 15 patients), 16 had
induction chemotherapy, and 10 had consolidation

chemotherapy.
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 consolidation. 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 documented 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).

### Table 1. Patients’ main characteristics

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

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

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

WRS during NR in Noncritically Ill Hematological Patients

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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 preexisting 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

**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.
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 limited. 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 hematological 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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References


