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EDITORIAL

# Pulmonary infiltrates in patients with malignancies: why and how neutropenia influences clinical reasoning

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Over the last two decades, increased intensity of anticancer therapy in patients with solid tumours or haematological malignancies has translated into better survival [1]. Overall, more patients are being treated, the treatments they receive are more aggressive, and patients more often undergo stem cell transplantation [2]. The result is an increase in the number of cases of patients with neutropenia [3].

Neutropenia is a decrease in circulating neutrophil counts in the peripheral blood. An absolute neutrophil count of 1,000–1,500 cells·mm$^{-3}$ defines mild neutropenia, 500–1,000 cells·mm$^{-3}$ defines moderate neutropenia, and <500 cells·mm$^{-3}$ defines severe neutropenia. In patients with pneumonia or acute respiratory failure, neutropenia may influence the clinical reasoning in three different ways.

First, although neutrophils are believed to be pivotal in the pathophysiology of acute respiratory distress syndrome and acute lung injury, these conditions can occur in neutropenic patients, as shown by the clinical and experimental literature [4–6]. In addition, respiratory deterioration during neutropenia is probably due to complex interactions between resident macrophages and migrated neutrophils sequestered in the lung interstitium, with upregulation of pro-inflammatory cytokines such as tumour necrosis factor-α and interleukin-1β [7, 8]. Exogenous granulocyte colony-stimulating factor may promote respiratory deterioration during neutropenia recovery [7, 9]. Macrophage deactivation may occur during granulocyte colony-stimulating factor therapy [10, 11], and granulocyte colony-stimulating factor may play a role in the upregulation of anti-inflammatory mediators, despite its ability to exacerbate lung injury [12].

Second, the type of immune dysfunction is one of the main clues to the cause of lung infiltrates [13]. In a recent cohort of 326 adult patients undergoing autologous stem cell transplantation, the risk of pneumonia was higher in patients who had myeloma or severe neutropenia for >7 days [14]. In addition, pneumonia is associated with an increased risk for septic shock and mortality [15]. In allogeneic stem cell transplantation, pulmonary complications are the events associated with the highest fatality rates, and pneumonia risk is highest after unrelated donor allogeneic peripheral blood stem cell transplantation [16]. Bacterial infections account for most cases of lung involvement in neutropenic patients [17]. The risk of bacterial infection is related to both the severity and the duration of the neutropenia [18]. Because laboratory techniques lack sensitivity in these patients, who routinely receive empirical antibiotics, the diagnosis usually relies on clinical data only [19]. Fungal infections should be considered only in patients with severe or prolonged neutropenia, immunosuppressive therapy to control graft *versus* host disease and, perhaps, those receiving targeted therapy such as rituximab [20].

Third, the prognostic significance of neutropenia itself has been controversial for years. In this issue of the *European Respiratory Journal*, ALIBERTI *et al.* [21] compare clinical outcomes of cancer patients admitted for community-acquired pneumonia with (n=73) or without (n=135) neutropenia. Overall, community-acquired pneumonia patients with cancer were found to have higher mortality rates than community-acquired pneumonia patients without cancer. However, among cancer patients, neutropenia did not influence time to clinical stability, length of hospital stay or in-hospital mortality. The study by ALIBERTI *et al.* [21] is in agreement with most of the studies reported over the last decade, in which neutropenia has supplied no prognostic information in cancer patients with acute respiratory failure [22, 23], even those requiring mechanical ventilation [24, 25]. However, neutropenia has been associated with outcomes in studies focusing on the overall population of critically ill cancer patients [26–28]. Several factors may explain why neutropenia is no longer associated with death in cancer patients admitted to the intensive care unit for acute respiratory failure. 1) As early studies discouraged the use of life-supporting treatments in patients with acute respiratory failure and malignancies [29, 30], neutropenic patients were perhaps less often referred to emergency departments. Therefore, neutropenic patients selected for inclusion in the Community-Acquired Pneumonia Organization database may not represent the actual picture of all neutropenic patients with community-acquired pneumonia. However, major advances in both cancer and intensive care unit management make these early studies obsolete [31]. 2) No information is available regarding the duration of neutropenia or the timing of neutropenia recovery. The results of ALIBERTI

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*et al.* [21] come chiefly from patients with solid tumours, which are usually associated with far shorter chemotherapy-induced neutropenia duration (<5–7 days) than haematological malignancies. Different results would perhaps have been obtained in patients with refractory neutropenia or in recipients of allogeneic stem cell transplants [32, 33]. Therefore, the prognostic information may lie not in the presence of neutropenia but in the type of underlying malignancy and treatment. 3) The chemotherapy response (*e.g.* remission) has not been reported. Patients receiving potentially curative chemotherapy are less likely to have treatment-limitation decisions than patients receiving palliative chemotherapy. Thus, although neutropenia develops in both groups, the use of life-supporting treatments may differ. It is of the utmost importance to offer full-code management, including life-supporting interventions, to patients at the earliest phase of their malignancy and to those receiving potentially lifespan-extending treatments [34]. In patients under palliative care, the management of life-threatening complications during neutropenia should strike the optimal balance between benefits from interventions and risks of severe quality-of-life alterations. In this situation, the decision to use life-supporting treatments should be based on the patient's preferences and values [35].

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