Acute Respiratory Failure in Patients with Hematologic Malignancies

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KEYWORDS

• High-resolution computed tomography • Immunocompromised • Noninvasive tests • Bronchoalveolar lavage

KEY POINTS

- Acute respiratory failure in patients with hematologic malignancies is frequent and associated with high mortality.
- Early recognition of acute respiratory failure in this population is necessary for improving outcomes.
- The diagnostic strategy for critically ill patients with hematologic malignancies differs from that in patients not admitted to the intensive care unit because of a different risk/benefit ratio of bronchoscopy and bronchoalveolar lavage (BAL) in deeply hypoxemic patients.
- Noninvasive diagnostic tests have a high diagnostic yield, whereas fiberoptic bronchoscopy with BAL adds limited diagnostic information.

INTRODUCTION

In immunosuppressed patients with cancer, the development of acute respiratory failure (ARF) is a common event. Overall, 15% of patients with hematologic malignancies present with a pulmonary event during the course of the disease and up to half the patients with prolonged neutropenia (ie, induction of acute leukemia or recipients of allogeneic hematopoietic stem cell transplants) have a pulmonary complication.[1] ARF is the leading cause of admission to the intensive care unit (ICU) for patients treated for hematologic malignancies, followed by shock and neurologic failure.[2–4] Etiologies of ARF are numerous and include pulmonary infections, complications of chemotherapy or of new anticancer drugs, or specific pulmonary involvement by the malignancy. In 20% of the cases, more than 1 cause is identified.

In critically ill hematology patients, survival after ICU management has greatly improved over the last 2 decades, thanks to a better selection of the patients eligible for intensive care and improvements in cancer treatments and in ICU management.[5–9] However, the need for intubation and invasive mechanical ventilation remains, and is associated with a 60% in-hospital mortality because it may reflect the subset of the sickest patients who also have several associated organ dysfunctions, including shock or renal, brain, or liver dysfunction.[2] Great hopes were prompted by the use of noninvasive mechanical ventilation (NIV) in this population,[5,10] but subsequent studies

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showed controversial results.[11–13] Recently, NIV was shown not to be superior to standard oxygen therapy in a multicenter prospective randomized study,[14] and NIV may be associated with an increased risk of intubation and death.[15]

Survival after ICU management is also linked to the early recognition of ARF and early transfer to the ICU.[3,16,17] Studies have shown that ARF from an undetermined cause was associated with higher mortality.[18,19] However, in this population, causes of ARF can be multifactorial and making an appropriate diagnosis may be very difficult. In an autopsy series of hematopoietic stem cell transplant recipients, only 28% of diagnoses were made before death.[20] Rapid and appropriate treatment of all possible causes of ARF is the key to improved outcome.

This article focuses on the clinical approach and diagnostic strategies for ARF in patients with nonpulmonary malignancy, specifically those with hematologic malignancies.

CLINICAL APPROACH

The first step is to recognize early signs of ARF in the hematology ward so early transfer to the ICU may be considered. Early recognition of ARF in this population is the key for improving outcomes.[16,17].

Some investigators described early criteria to diagnose early acute lung injury (EALI) before the onset of ARF and acute lung injury and in order to start a specific treatment as early as possible.[21] The EALI score is based on oxygen requirement (1 point for an oxygen requirement >2–6 L/min or 2 points for >6 L/min), respiratory rate (1 point for a respiratory rate $\geq$30 breaths/min), and immune suppression (1 point for baseline immune suppression). A score greater than or equal to 2 identified patients who progressed to acute lung injury requiring positive pressure noninvasive ventilation with 89% sensitivity and 75% specificity. This score could be easily used by clinicians for patients in hematology wards. More complex scores have been described but are difficult to use in practice.[22]

The second step is to make a rapid and accurate diagnosis of the underlying cause. However, the clinical lung examination is not specific and additional pulmonary signs should be carefully screened. Therefore, a systematic and rationalized approach is necessary to narrow the differential diagnosis.

The authors previously described a clinical approach described by the mnemonic, DIRECT[1] (**Box 1**), to assist clinicians in determining ARF cause and guide initial treatment and complementary investigations.[23] It is based on the analysis of the delay since the onset of malignancy or hematopoietic stem cell transplant, or the delay since initial effective antibiotic therapy or chemoprophylaxis; the pattern of immune deficiency; the radiographic appearance; the experience and knowledge of the literature; the clinical picture (ie, septic shock, skin rash, or associated extrapulmonary symptoms); and patterns observed on the computed tomography (CT) scan.

Box 1
DIRECT criteria for identifying the most likely causes of acute respiratory failure in patients with cancer

Delay since malignancy onset or HSCT

Immune deficiency pattern

Radiographic appearance

Experience and knowledge of the literature

Clinical picture

HRC**T** findings

Abbreviations: HRCT, high-resolution computed tomography; HSCT, hematopoietic stem cell transplantation.

Also, given advances in patient management and the many new anticancer and antiinflammatory drugs, managing patients in perfect synchrony with hematologists is an obvious requirement. Some of the adverse events of these recently developed agents are still to be described. For example, idelalisib is now described to be responsible for acute pneumonitis[24] and anti–tumor necrosis factor drugs have been associated with an increased risk of nocardiosis.[25]

DIAGNOSTIC STRATEGIES

After a careful clinical examination, patients can be classified based on the clinical pulmonary pattern (focal consolidation vs diffuse crackles, cardiac insufficiency vs noncardiac pulmonary involvement, pleural effusions, extrathoracic findings). A careful approach to additional diagnostic studies must be guided by the clinical findings and the DIRECT screening.

Transthoracic Echocardiography

This test should be obtained in order to rule out cardiogenic pulmonary edema.[26] Performing echocardiography also allows examination of the lungs and pleura, which is helpful when it is not feasible for the patient to undergo lung high-resolution computed tomography (HRCT).[26,27] Note that, because of vascular toxicity from chemotherapy and diastolic cardiac insufficiency, only a