Antonio M. Esquinas · S. Egbert Pravinkumar
Ayman O. Soubani *Editors*

Mechanical Ventilation in Critically Ill Cancer Patients

Rationale and Practical Approach

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Editors

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Editors
Antonio M. Esquinas
Intensive Care and Non Invasive
Ventilatory Unit
Hospital Morales Meseguer
Murcia, Spain

Ayman O. Soubani
Wayne State University School of Medicine
Detroit, Michigan, USA

S. Egbert Pravinkumar
Division of Anesthesiology and
Critical Care
The University of Texas
M.D. Anderson Cancer Center
Houston, Texas, USA

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To all our patients, to whom we will always owe at least a little hope

Preface

Survival of critically ill cancer patients admitted to intensive care unit (ICU) for management of acute deteriorations related to underlying malignancy, infections, and treatment-related organ dysfunctions is improving worldwide. In particular outcomes of cancer patients receiving mechanical ventilator support have improved given the timely optimal diagnostic and therapeutic management of critically ill cancer patients with respiratory failure. Advances in the care of deteriorating organ functions in cancer patients, early recognition of acute clinical decline and admission to ICU, use of rapid response teams, and clinical practice algorithms play an important role in the positive outcome of these patients. Furthermore, advances in ventilator support devices, aggressive structured and standardized weaning from mechanical ventilation and intravenous sedatives, use of noninvasive mechanical ventilatory support, and education of health care providers have significantly contributed to the improved survival of cancer patients in the ICU.

This book is focused on the care of cancer patients in the ICU given the increased incidence of cancer and related critical illness. Experts from various countries have contributed to the development of this book by sharing their expertise in their specific area of practice. The book provides an in-depth understanding of the rationale and practice of mechanical ventilatory support in critically ill cancer patients. The book is unique in that it has an international panel of experts focused in the clinical care of cancer patients with critical illness.

The lack of a wider international perspective on ventilatory support in cancer patients triggered the need for this textbook. The chapters are structured in such a way that the reader would appreciate the different aspects of ventilator support such as pre-ICU support, types of ventilatory support, and postoperative ventilatory support. Chapters on ICU end-of-life care, withdrawal of mechanical ventilator support, and health care cost/resource utilization have been included to provide the reader a realistic and wider perspective of ventilatory support for cancer patients.

The book will aid in acquiring knowledge and understanding of ventilatory support for critically ill patients with both solid and hematological malignancies. Coordinating the creation of a book with international authors, like this book, is of no easy task; nevertheless, it has resulted in compilation of knowledge from international authors for a broader view in the management of critically ill cancer patients. We hope that the reader would find this book not only interesting but as a resource of practical knowledge.

The editors would like to acknowledge the willingness of these experts in sharing their experience and knowledge in this area. We would also like to thank Ms. Madonna Samuel and Andrea Ridolfi with Springer Publishing Group for their support throughout the process.

Murcia, Spain Antonio M. Esquinas
Houston, TX, USA S. Egbert Pravinkumar
Detroit, MI, USA Ayman O. Soubani

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Part I

Background and Therapeutic Procedures in Critically Ill Cancer Patients

1 Epidemiology of Mechanical Ventilation and Acute Respiratory Failure in Cancer Patients

Dulce Apolinário

Abbreviations

ARDS	Acute respiratory distress syndrome
ARF	Acute respiratory failure
ICU	Intensive care units
NIV	Noninvasive mechanical ventilation
TRALI	Transfusion-related acute lung injury

1.1 Introduction

The number of cancer patients has increased over the last decades, as a result of survival gains achieved by intensive treatments, with an estimated prevalence for 2012 of 32.6 million persons alive who had been diagnosed with cancer in the previous 5 years [1].

With the improved survival of these patients, the complications associated with the oncologic disease and its treatment have also increased, being the lung the organ most frequently involved, resulting in respiratory failure [2].

This chapter reviews the epidemiology and major causes of acute respiratory failure (ARF) in adult patients with malignancies requiring ventilatory support.

D. Apolinário
Resident, Pulmonology Service, Centro Hospitalar de Trás-os-Montes e Alto Douro, Vila Real, Portugal
e-mail: dulce.apolinario@sapo.pt

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1.2 Discussion and Analysis of the Main Topic

1.2.1 Acute Respiratory Failure in Cancer Patients

Cancer-related complications or treatment-associated side effects can lead to lung damage that can result in respiratory failure [2].

ARF requiring mechanical ventilation is a leading cause of admission to intensive care units (ICU) for patients with malignancies, who are actually more often admitted to the ICU for respiratory complications than the other ICU patients [3]. The frequency of ARF ranges from 5 to 50% in patients with hematologic and solid malignancies and from 42 to 88% among hematopoietic stem cell transplant recipients [2, 4].

This condition has a poor outcome in cancer patients, with high mortality rate, mainly in patients with ARF requiring mechanical ventilation. In patients with hematologic and solid malignancies who require mechanical ventilation, the mortality is 50% and 75%, respectively [2]. Among hematopoietic stem cell transplant recipients requiring mechanical ventilation and ICU admission, the mortality rate is approximately 85% [2]. Notwithstanding, this clinical scenario has changed in the late years, and improved survival rates have been reported: in a Sepsis Occurrence in Acutely Ill Patients substudy, the outcome of patients with solid cancer was similar to ICU patients without cancer, with ICU mortality rates of 20% and 18%, respectively [3]; still, patients with hematological cancer had a worse outcome with the highest hospital mortality rate (58%) [3]. Investigators attribute the increased survival to advances in oncology, hematology, and critical care, in conjunction with more appropriate selection of cancer patients for ICU admission [2, 4].

Various infectious and noninfectious causes, both by complications of the own cancer and by side effects associated with the therapies, can lead to ARF in these patients [2].

1.2.1.1 Infectious Causes

Cancer patients have an increased risk of pulmonary infections due to defects in humoral and/or cell-mediated immunity, neutropenia, use of immunosuppressant drugs, higher risk of aspiration, frequent exposure to antibiotics, and prolonged hospitalizations [2]. The pulmonary infections are the most frequent cause of ARF in patients with cancer, especially in those with severe comorbidities, underlying hematologic malignancies or those undergoing chemotherapy [2, 4].

The majority of pneumonias have bacterial etiology (47%), being the most frequently documented pathogens the gram-positive cocci (40%), like *Streptococcus pneumoniae* (20%), other streptococci (12.5%), and *Staphylococcus aureus* (7.5%); gram-negative bacilli (49%) such as *Escherichia coli* (10%), *Enterobacter cloacae* (10%), Klebsiella pneumonia (4%), *Pseudomonas aeruginosa* (16%), and *Haemophilus influenza* (4%); gram-negative cocci (1%) including *Neisseria sp.* (1%); and intracellular bacteria (10%) like *Legionella pneumophila* (5%), *Mycoplasma pneumonia* (2.5%), *Coxiella burnetii* (1%), and *Chlamydia pneumoniae* (1%) [5].

Opportunistic pulmonary infections are also common in these patients (31%), such as invasive pulmonary aspergillosis (31%), respiratory viral infections (28%), *Pneumocystis jirovecii* pneumonia (27.5%), tuberculosis (5%), mucormycosis (4.5%), *Cytomegalovirus* infection (1.5%), fusariosis (1.5%), *Scedosporium* sp. infection (1%), and *Toxoplasma gondii* infection (1%) [5]. Fungal pneumonia is more frequent in the setting of prolonged neutropenia, corticotherapy, broad-spectrum antibiotherapy, or underlying leukemia or lymphoma [2]. Community respiratory viruses have also been recognized as a cause of pneumonia among hematopoietic stem cell transplantation recipients and patients with hematologic malignancies, more frequently the influenza (33%), respiratory syncytial (31%), and parainfluenza (27%) viruses [6].

The infections are also the major cause of primary acute respiratory distress syndrome (ARDS) in patients with cancer (65.9%), including bacterial infection (58%) and invasive fungal infections (42%), such as invasive pulmonary aspergillosis and *Pneumocystis jirovecii* pneumonia [7]. In patients with septic shock, secondary ARDS can also occur (22.4%) [7].

1.2.1.2 Noninfectious Causes

Although the noninfectious etiology of ARF in cancer patients is less frequent, with values around 22%, and only 7.6% in the subgroup of patients with ARDS, there are numerous causes for it, and the most frequently described findings are pulmonary edema (49%) and pulmonary infiltration by the malignancy (49%) [5, 7].

One of the noninfectious causes is the decompensation of concurrent respiratory and cardiovascular diseases, which may lead to or worsen respiratory failure [2].

Another cause of ARF in these patients is the transfusion-related acute lung injury (TRALI), which usually manifests itself as lung noncardiogenic pulmonary edema in the sequence of blood product transfusion [2].

Antineoplastic agent-induced lung injury is a major problem for cancer patients having a broad spectrum of manifestations (bronchospasm, hypersensitivity reactions, lung fibrosis, diffuse alveolar hemorrhage, acute interstitial pneumonitis, ARDS, capillary leak syndrome, and organizing pneumonia) [2, 4]. In patients who have previously received radiation to the chest, radiation-induced lung injury may occur and is manifested by an early acute phase in the form of pneumonitis (radiation pneumonitis) and a late phase of pulmonary fibrosis [2].

Venous thromboembolism, manifested as either deep venous thrombosis or pulmonary embolism, is a frequent cancer-related medical disorder, present in about 7.8% of patients hospitalized with cancer, especially with advanced malignancies, renal carcinoma, pancreatic, gastric, and brain tumors [8].

In thrombocytopenic patients with acute or chronic leukemia or multiple myeloma, and in recipients of hematopoietic stem cell transplantation, alveolar hemorrhage is also a frequent cause of respiratory failure [2].

The paraneoplastic syndromes, such as myasthenia gravis, Lambert-Eaton myasthenic syndrome, or Guillain-Barré syndrome, can cause respiratory failure due to respiratory muscle weakness, as well as upper airway compromise caused by weakness of the facial, oropharyngeal, and laryngeal muscles [2].

The disease own progression can lead to ARF by direct neoplastic involvement of the respiratory tract, resulting in upper or lower airway obstruction, or even to disseminated parenchymal disease or lymphangitis [4].

In patients undergoing thoracic cancer surgery, ARF may also occur postoperatively due to atelectasis, pneumonia, pulmonary edema, and development of bronchopleural fistula [2].

1.2.2 Mechanical Ventilation in Cancer Patients

Many cancer patients with ARF need mechanical ventilation support, with frequencies of 62.2% in solid tumors and 69.6% in hematological cancers [3]. The identified risk factors for invasive mechanical ventilation in subjects with malignancies admitted for ARF are respiratory disease severity (oxygen flow required and number of quadrants involved on chest x-ray) and hemodynamic dysfunction at ICU admission [9].

Although the prognosis of these critically ill patients is disappointing, especially if they require endotracheal intubation, it is demonstrated that half of the cancer patients with good performance status and nonprogressive disease requiring ventilator support survive, so they should receive full intensive care [10].

In the last years, noninvasive mechanical ventilation (NIV) has been increasingly used as an alternative to invasive ventilation, as it has the benefits to reduce the infectious complications in patients affected by hematologic cancers or those with immunosuppressant drugs, avoid intubation-related trauma, enhance patient comfort, and reduce the need for sedation [2, 4]. Nonetheless, NIV has to be used in appropriate situations because its failure has been associated with increased mortality [4]. NIV may also be a reasonable option in cancer patients with respiratory failure who have refused endotracheal intubation or have a “do not intubate” order [2].

1.3 Conclusion

ARF is frequent in cancer patients due to cancer-related complications and treatment-associated side effects. Various etiologies can lead to ARF in these patients, conducting to diagnosis and management challenges. The pulmonary infections are the most frequent causes, but many noninfectious causes are described, such as decompensation of concurrent respiratory and cardiovascular diseases, pulmonary drug toxicity, radiation-induced lung injury, TRALI, antineoplastic agent-induced lung injury, venous thromboembolism, alveolar hemorrhage, paraneoplastic syndromes, disease progression with airway obstruction, disseminated parenchymal disease or lymphangitis, and complications of thoracic cancer surgery.

Regardless of the cause, ARF is a severe condition and frequently requires ventilatory support and ICU admission. It is still associated with a poor outcome and high mortality, despite the general improved outcome over the last decade.

1.4 Key Major Recommendations

- ARF remains a frequent and severe complication in cancer patients. Despite most of the times being of infectious origin, there are many other possible causes, the knowledge of its epidemiology and main etiologies being essential.
- Many cancer patients with ARF will need mechanical ventilation support and ICU admission.

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2 Breathlessness in Advanced Cancer Patients: Protocols and Recommendations

Manuel Sánchez Cánovas, Juan Gutiérrez Mejía,
Alberto Carmona Bayonas, and Paula Jiménez-Fonseca

2.1 Introduction: Definition and Epidemiology

Breathlessness and dyspnea are common terms used to describe a conscious, unpleasant, intense, and frightening experience related to shortness of breath. Patients describe breathlessness as suffocating, choking, or tightness of breath. It can be described along three dimensions: (1) air hunger, a need to breathe while being unable to increase ventilation; (2) effort of breathing, physical tiredness associated with breathing; and (3) chest tightness, feeling of constriction and inability to breathe in and out [1, 2].

This is a frequent and distressing symptom in cancer patients; however, it is often overlooked [3]. In fact, for many people, breathlessness is tolerated and sublimated, and there is evidence of massive underreporting of the symptom [4].

Thus, epidemiological data is unlikely to reflect objectively much information. Although the case series are heterogeneous, depending on the baseline characteristics of patients and tumors, it may be present in around 20–40% of cancer patients at the diagnosis of advanced disease, with symptoms prevalence reaching 70% in the last 6 weeks of life. Therefore, breathlessness is the second most common reason for starting palliative sedation.

There is no correlation between objective measurements of dyspnea and the experience of breathlessness perceived by the patient. It is a personal subjective

M.S. Cánovas • A.C. Bayonas
Hematology and Medical Oncology Department, Hospital Universitario Morales Meseguer (Murcia), Calle Marqués de los Vélez s/n, Murcia, Spain

J. Gutiérrez Mejía, M.D., M.H.Sc. (Bioethics) (✉)
National Institute of Medical Sciences and Nutrition, Salvador Zubiran, Mexico City, Mexico
e-mail: jgtzm@hotmail.com

P. Jiménez-Fonseca
Medical Oncology Department, Hospital Universitario Central de Asturias (Oviedo), Oviedo, Spain

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experience colored by social and physiological unique characteristics and shaped under cognitive, sensory, behavioral, and emotional components from each patient. This explains why breathlessness can only be correctly interpreted by sufferers.

On the other hand, the experience of caregivers who are looking after a patient with dyspnea is in general negative, exhausting, and abundant in extreme tension that gives place to poor sleep and anxiety. Thus, appropriate care of advanced cancer patients should also take into account carers' needs and well-being. Recently the term "total dyspnea" has being proposed in consideration of the complexity of the symptom and its multiple dimensions affecting all domains of quality of life (e.g., emotional, functional, social, spiritual, etc.) because of their deep consequences [1, 5].

2.2 Etiology and Pathogenesis

Breathing is autonomously regulated at the respiratory centers located in the medulla and pons, triggered by specialized neuron networks under the major influence of the partial pressure of carbon dioxide (PCO_2) concentration and pH at the surrounding cerebrospinal fluid. Higher level of control is found at the motor cortex, which allows for transient voluntary changes of breathing patterns. The motor cortex interacts with the sensory cortex, integrating information of afferent receptors via the glossopharyngeal and the vagus nerve. Normally this information should be complementary and similar.

The origin of breathlessness experience is still matter of research. It is a consequence of a complex integration from multiple receptors along the respiratory and cardiovascular system at different neurologic levels [6]. There are several theories on the origin of dyspnea:

1. According to the corollary discharge theory, a copy of the respiratory commands is sent from the motor to the sensory cortex, informing other regions of the brain of the respiratory pattern and producing conscious awareness of the respiratory effort.
2. Dyspnea may also arise by the existence of mismatch between the output of the respiratory controllers, in the motor cortex and afferent signals arriving from the lungs and chest wall receptors that gauge the response of the effector ventilator pump, which is mediated through the phenomenon called efferent-reafferent dissociation.
3. The experience may also be directly provoked by mechanoreceptors and chemoreceptors, centrally and peripherally, that influence the perception of "chest tightness and air hunger" [3], as follows:
   (a) Peripheral chemoreceptors located in the carotid and aortic bodies respond to the partial pressure of O_2 in arterial blood (PaO_2), PCO_2, and pH serum changes. Carotid chemoreceptors are more sensitive than aortic bodies to variations of these parameters.

(b) Skeletal muscles also have metaboreceptors that respond to increasing levels of tissue metabolites like lactate, produced during anaerobic metabolism. Exercise-induced dyspnea in normal individuals may be explained by this mechanism, independently of the occurrence of hypoxemia or hypercapnia.
(c) Receptors in the oral mucosa, nasal airway, and facial receptors at the sensitive territory of trigeminal nerves can be stimulated with airflow, so that their stimuli decrease breathlessness experiences and improve exercise tolerance in patients with chronic dyspnea.
(d) Other mechanoreceptors and chemical receptors have been detected at the lower airway, some represented by unmyelinated nerve endings (C-fibers) responding to irritant signals and bronchoconstriction, while others as stretch receptors from parenchymal zones sensitive to distention, and finally pressure receptors from the airway walls and alveolar walls (J receptors) combined with pulmonary vascular receptors responding to high vascular pressures have also been related to breathlessness.
(e) Chest wall receptors located in joints, tendons, and intercostal muscles decrease breathlessness when stimulated.

Functional brain image has shown the activation of neurologic areas in the anterior insula and posterior cingulate gyrus induced by breathlessness; these areas have been related with pain perception which may explain why opioids have an effect in the palliative treatment of dyspnea [7–9]. The most frequent cause of dyspnea in cancer patients would be the existence of a primary lung tumors or the existence of pulmonary metastases. However, the origin of this symptom may be varied:

1. Direct effect of cancer; this section encompass several pathogenic mechanisms:
   (a) Obstruction of the airway: it can be the result of a primary tumor, lymph nodes, or metastatic disease. However, breathlessness can also have its origin in the excess of secretions associated to some tumor subtypes or the infiltration of vocal cords.
   (b) Injuries of the lung parenchyma (tumor, infections, radiotherapy, etc.).
   (c) Vascular syndromes, such as symptomatic pulmonary embolism in immobilized patients or thrombogenic tumors, superior vena cava syndrome (especially in small-cell lung cancer or lymphoma), etc.
   (d) Pleural effusions (malignant mesothelioma or metastases from other sites).
   (e) Weakness of the respiratory muscles; secondary to cachexia, electrolytic alterations, or neuromuscular disease or paraneoplastic syndromes (e.g., Guillain-Barre, Eaton-Lambert syndrome, etc.).
   (f) Decrease in the chest wall distensibility, which could be secondary to massive ascites or visceromegaly. This is typical of hepatocellular carcinomas, peritoneal metastases (e.g., gastric tumors), or ovarian cancer.
   (g) Other possible causes that could be included within this group would be systemic alterations such as anemia, acidosis, and neuropsychiatric disorders (depression, anxiety disorders, etc.), which are very common in cancer patients.

2. Effect of antineoplastic therapy (iatrogenic adverse events):

    (a) Cancer therapy constitutes a potential cause for dyspnea; specifically, both radiotherapy and chemotherapy (e.g., bleomycin, gemcitabine, everolimus, anti-PD1, etc.) can provoke pneumonitis, pulmonary fibrosis, cardiopulmonary toxicities, anemia, venous thromboembolic disease, cachexia, etc. Serious adverse events can contribute to the onset of dyspnea or the worsening of the previous health status.
    (b) It is expected that novel, emerging antitumor strategies such as immunotherapy or other targeted therapies may become a sources of respiratory distress in the cancer population. Therefore, it will be a challenge to develop effective management algorithms for these new modalities. Further research in this field is required to unveil the underlying physiopathological mechanisms, in order to prevent and manage these complications efficiently.
    (c) Finally, aggressive surgical approaches for lung primary tumors and metastases (e.g., lobectomy, pneumonectomy, etc.) can be a source of residual breathlessness, particularly in patients with prior vulnerabilities or chronic respiratory comorbidities.
3. Other contributing factors:

Chronic comorbidities (e.g., chronic obstructive pulmonary disease, cardiovascular disorders, bronchial hyperresponsiveness associated with asthma, etc.) are common in oncologic patients due the coexistence of multiple risk etiologic factors and increases in average life expectancy. In certain groups of patients, they may constitute the main causes for the onset or exacerbation of dyspnea.

2.3 Breathlessness Management in Oncological Patient: Diagnosis and Treatment

Concerning the palliative management of dyspnea, two basic fronts should be addressed:

(a) The etiologic approach: dyspnea has many causes involving either the breathing airways and lungs or the cardiocirculatory system. If we can identify them, they could be tackled with a targeted treatment (e.g., anticoagulants for pulmonary embolism, antibiotics, corticoids, etc.).
(b) The symptomatic strategy: dyspnea is per se a very disabling symptom for all patients, calling for an immediate therapeutic attitude regardless of the underlying etiology.

Obviously these dichotomies are two sides of the same coin, so both therapeutics should be resolved and approached at the same time. The key to distinguish which one should constitute our starting focus of attention should be given by the patient, taking into account that a number of severity criteria exist that need to be identified in patients with respiratory distress: tachypnea, altered mental status, tachycardia, hemodynamic

instability, and use of accessory muscles. Patients' prognosis and the potential reversibility of the respiratory syndrome should also be promptly elucidated.

The presence of severity criteria would force us to begin supportive care rapidly and should not lead to a delay in the establishment of palliative care management in these patients. This will not only impact on quality of life and anxiety, but it will also subsequently facilitate the realization of the necessary etiological studies.

In contrast, a patient who is apparently out of danger, and in situation of no severity, will mainly benefit from the identification of a causative factor to better target his treatment, without exempting us from controlling the symptoms that might present.

2.3.1 Etiologic Approach to Management

In general, the idiosyncrasy of cancer should not constitute an obstacle for the correct assessment in dyspneic patients. It is true that the differential diagnosis covers a wider range of possibilities in comparison with the general population, but the algorithm to follow does not include significant differences.

It will be crucial to evaluate the origin of our patient's dyspnea properly, since it will impact the management and outcomes in reversible conditions. Conducting a good anamnesis and thorough clinical examination will be the first step to identify the etiology and guide the subsequent workup. We show some examples in Table 2.1.

Table 2.1 Suggested workup in acute respiratory failure

Clinical findings	Diagnostic suspicion	Workup
Fever	Pneumonia	Chest X-ray
Sudden onset in immobilized subjects	Pulmonary embolism[a]	Computed tomography angiography
Abdomen distension	Ascites	Abdominal ultrasound
Unilateral auscultatory silence	Pleural effusions—pneumothorax	Chest X-ray
Facial and neck swelling	Superior vena cava syndrome	Chest CT scan
Normal oxygen saturation	Anxiety states	Not required
Neurological symptoms	Brain metastases	TC cerebral
Laryngeal stridor	Upper airway obstruction	Laryngoscopy
Wheezing	Bronchospasm	Chest X-ray (to discard associated complications)
Chemotherapy/radiotherapy	Pneumonitis	Chest X-ray
Lower extremity edema	Acute heart failure	Chest X-ray
Cachexia, other gastrointestinal complaints	Anemia, electrolytic alterations	Blood tests

[a]The risk of venus thromboembolism (VTE) is estimated to be fourfold higher in cancer patients compared with noncancer patients. VTE has been found to be an adverse prognosis factor in all stages of cancer [10]. In fact, it has been described as the second cause of death in cancer patients

Once we confirm each one of these diagnoses, management will be the specific for each entity. We would like to conclude this paragraph recalling that regardless the etiology and the requested workup, it could be essential for some patients to carry out an arterial gasometry in order to:

(a) Determine the severity of the event which has prognostic and therapeutic implications.
(b) Support the causative diagnosis of acute respiratory failure.

Of note, criteria for diagnosis of acute respiratory failure are based on laboratory and clinical findings. It is confirmed when the pressure of oxygen in arterial blood (PaO_2) is less than 60 mmHg, which is approximately equivalent to an arterial oxygen saturation of 90%, as measured by pulse oximetry.

Despite this approximate equivalence, pulse oximetry has a lower reliability in certain contexts in which it should not substitute an arterial blood gas analysis (serious anemia, jaundice, peripheral hypoperfusion, hypothermia, etc.) the former do not provide pH values or the partial pressure of carbon dioxide ($PaCO_2$), which is helpful in determining the origin of dyspnea, as displayed in Fig. 2.1.

There are some particular oncological fields whose management is essential to know in order to get better results in our patients:

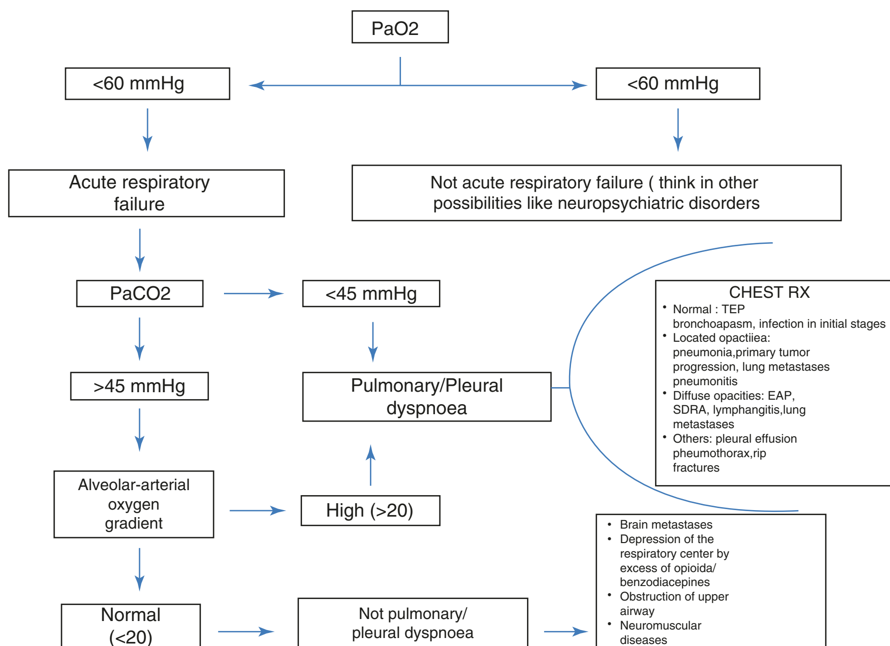

Fig. 2.1 Diagnostic algorithm for acute \ failure in cancer patients

2.3.1.1 Immunological Checkpoint Inhibition Agents (Targeting CTLA-4 and PD-1)

They are new therapeutic strategies whose use is increasing at different malignancies. This new group of medication is associated with immune-related adverse events. Examples related with breathlessness, have been described in sarcoidosis, organizing inflammatory pneumonia, or pneumonitis. The treatment of moderate (grade 2) or severe (grades 3–4) immune-related adverse events requires [11]:

- For patients with grade 2 toxicities, treatment with the checkpoint inhibitor should be withheld and should not be resumed until symptoms or toxicity is grade 1 or less. Corticosteroids (prednisone 0.5 mg/kg/day) should be started if symptoms do not resolve within a week.
- For patients experiencing grade 3–4 immune-mediated toxicities, treatment with the checkpoint inhibitor should be permanently discontinued. High doses of corticosteroids (prednisone 1–2 mg/kg/day) should be given. When symptoms subside to grade 1 or less, steroids can be gradually tapered over at least 1 month.

2.3.1.2 Bleomycin [12]

Bleomycin is associated with the four main types of pulmonary toxicities: subacute progressive pulmonary fibrosis, hypersensitivity pneumonitis, organizing pneumonia, and acute chest pain syndrome during rapid infusion. The risk appears to be higher in older patients and those with renal insufficiency.

Thoracic irradiation and concurrent administration of cisplatin at high doses may increase the risk. For patients with symptomatic pulmonary toxicity and evidence of impairment on pulmonary functions tests, the management consists in administration of systemic glucocorticoids (prednisone 0.75–1 mg/kg) and discontinuing bleomycin therapy.

2.3.2 Symptomatic Management

In patients with severe symptomatology or the aforementioned severity criteria, the control of the dyspnea becomes a fundamental objective. Before moving toward any etiologic management, the stabilization of our patient will be the priority. Cancer patients can decompensate for various reasons, similar to subjects with other chronic conditions.

Certain types of advanced cancer are not necessarily a synonymous of imminent death, and novel therapies are rapidly changing the landscape of tumors that were previously considered incurable. It is very easy to fall into the mistake of evaluating patients' health status and prognosis superficially which may consequently entail a definitive sedation or limitation of therapeutical effort.

There is also a debate on whether cancer patients are subsidiary to intensive care unit (ICU) admission or not. For a long time, an ICU admission has been denied to most patients with advanced tumors. Fortunately, this perception is beginning to change, and the label of a cancer diagnosis should not preclude the objective and accurate perception of the disease we are confronting.

It is mandatory to carry out a comprehensive assessment of the oncologic antecedents, including the evolution cancer, prognosis, possibilities of tumor control, etc., which should also entail the necessity of updating medical records with anticipated recommendations in case of acute respiratory failure. These anticipated orders as well as the presence of other chronic comorbidities and the acute baseline situation will help us to estimate medium-term prognosis and therefore to decide, in conjunction with the intensivists, whether an ICU admission is advisable. The basic clinical and laboratory criteria that would require an assessment by the ICU specialists include the following:

1. Shock or arterial blood pressure <90 mmHg
2. Severe dysfunction of two or more systems (including the respiratory)
3. Severe acidosis: $pH < 7.25$
4. PaO_2/FiO_2 ratio <200
5. Serious hypercapnia encephalopathy (Glasgow < 12)

Within the symptomatic management, we have three branches: the ventilatory support, non-pharmacological management, and pharmacological support.

2.3.2.1 Ventilatory Support

Oxygen therapy is recommended in hypoxemic patients with dyspnea [13]. There is no benefit of adding oxygen for cancer patients if they are not hypoxic. Hypoxemia is in general a weak stimulus for dyspnea. It is possible to obtain relief in symptoms associated with breathlessness by facilitating a flow through nasal prongs using room air, maybe as consequence of sensory stimulation. Because of the burdens in oxygen therapy and impact on patients and carers, initiation of this therapy should be clearly identified [14].

The venous blood gas and the patient's history will determine which type of oxygen therapy technique will be the most appropriate. It will be indicated always that hypoxemia is objectified by arterial blood gases:

(a) Nonspecific technique of oxygen therapy is a contraindication for patients who are not chronic CO_2 retainers (e.g., COPD), despite the existence of $PaCO_2$ elevations due to the acute respiratory disorder.
(b) Chronic CO_2 retainers that maintain high basal $PaCO_2$ must be ventilated with noninvasive mechanical ventilation (NIV), such as bi-level positive airway pressure (BiPAP) or even orotracheal intubation if the patients meet the criteria for ICU admission, because of the high risk of hypercapnic encephalopathy syndrome. Only consider intubation at the assumption of poor tolerance to BiPAP, high-flow nasal cannula oxygen therapy (4 L/min) or venturi masks (Ventimask) at (e.g., fraction of inspired oxygen (FiO_2) set at 35% and 6 L/min)

The increment on the complexity of devices for ventilatory support (nasal prongs, Ventimask, large-reservoir venturi masks, BiPAP, orotracheal intubation, etc.),

increasing the FiO_2, will rely on the SaO_2, as per the pulse oximetry (useful for monitoring and tracking).

High flow nasal cannula is suggested to be used early in patient's refractory to standard oxygen therapy with hypoxemia. Usually it is very well tolerated and allows patient to talk, eat, and avoid tight masks associated with NIV [13]. Noninvasive positive pressure ventilation such as BiPAP is indicated in patients with hypoxemia and hypercapnia, in which a substantial improvement is usually seen in the first hours. The success of this treatment is related with the "early" use and experience of the involved staff [15].

The clinical benefit of the BiPAP has been strongly demonstrated in different situations of dyspnea/acute respiratory failure, such as respiratory acidosis, advanced neuromuscular disease, immunocompromised patients, severe acute cardiogenic pulmonary edema, etc. Actually NIV has also a place in the palliation of patients at the end of life situations, by the following reasons:

(a) It reduces the ventilatory work facilitating breathing movements, by which the dyspneic sensation diminishes.
(b) NIV decreases the needs for opioids, which promotes a higher level of consciousness, which is usually regarded by palliative care teams as prerequisite for a good death, since it allows saying goodbye to loved ones.

2.3.2.2 Non-pharmacological Treatment

Non-pharmacological treatment is focused on cognitive, sensitive, emotional, and behavioral areas. This approach is based on models of symptom perception that establish stages of appraisal, from the interpretation of symptoms through patients' lens to the asignment of meaning according to their values, beliefs, previous experiences, expectations, motivations, and personality.

This type of treatment should be started early, if possible before the pharmacological options, and continued even when that medication has started. It is very important for the patient to have certain control over symptoms. Patient's experience is affected by the social context and behavior of others; this is the reason why relatives and other caregivers should be involved in the same educating process. Several interventions have been suggested, like:

(a) Sitting and using good posture; especially in this last point, patients should always acquire whatever position is more comfortable for them even against of what carers believe is a "better position." Pacing movements in a slower execution and dividing the job in several steps will help in symptoms control.
(b) Learning breathing strategies is very useful; one of the best techniques is pursed lip breathing that allows patients to increase tidal volume and vital capacity, improving the removal of CO_2, decreasing respiratory rate, and reducing hyperinflation, while improving dyspnea as a consequence [3, 16].
(c) Using a fan or opening a window, in order to produce a cold airflow that stimulates facial receptors in trigeminal territories.

2.3.2.3 Pharmacologic Support

Opioids are the main treatment of breathlessness in advanced cancer patients. They are usually used by oral or intravenous routes as the first option. However, studies looking for other possible routes of administration have been conducted. It should be noted the lack of efficacy observed for nebulized opioids. However the sublingual application seems to constitute an efficacious therapeutic option effective with fewer side effects in comparison with other systemic alternatives.

The mechanism of how opioids decrease breathlessness is not well known. Opioid receptors are localized at different levels of the cardiovascular, respiratory and central nervous systems. Opioids are safe when prescribed under a stepped incremental-reassessed dose guideline; their use helps to reduce the unpleasantness of dyspnea. Recommendations should be evaluated in an individual case-by-case approach and adjusted according to patient response; clinical judgment should always precede any treatment decision. Patients with prior chronic opioid treatment for pain may need different doses from that of opioid-naïve patients.

The adverse effects associated with opioid treatment include drowsiness, nausea, vomiting, and constipation compared with the placebo. Morphine is recommended over all other types of opioids, by oral or parenteral administration as the first option for symptom control. It should be used carefully in patients with severe renal insufficiency (Table 2.2).

Benzodiazepines have classically been considered as a therapeutic option for the control of dyspnea at the same level of opioids. Different clinical trials have made clear that this single-drug group is superior to opioid when the cause of dyspnea is neuropsychiatric, for example, in anxiety disorders [18]. Benzodiazepines cause more drowsiness in comparison with placebo, but less than with morphine. These results justify the consideration of benzodiazepines as a second line for refractory

Table 2.2 Opioid doses and administration in cancer patients with dyspnea

Clinical setting		
Naïve patients with mild dyspnea	Naïve patients with severe dyspnea	Patients with severe COPD (start at 50% of the above doses and titrate 25% every 24 h as needed)
Hydrocodone 5 mg orally every 4 h	Morphine sulfate 5 mg orally every 4 h	Increase baseline dose by 25–50% and reassess every 24 h [17]
Codeine 30 mg orally every 4 h	Oxycodone 5 mg orally every 4 h	Morphine regular opioid dose +1/6 of daily opioid intake
Morphine 2.5–5 mg/4 h orally and 1–2.5 mg /4 h subcutaneous	Breakthrough management considers an equivalent dose every 1–2 h	Hydromorphone regular opioid dose +1/6 of the daily opioid intake
Hydromorphone 1.3 mg/4 h orally or 0.2–0.5 mg/4 h subcutaneous	Titrate in increments of 50–100% every 24 h as needed	
Breakthrough management consider an equivalent dose every 1–2 h		

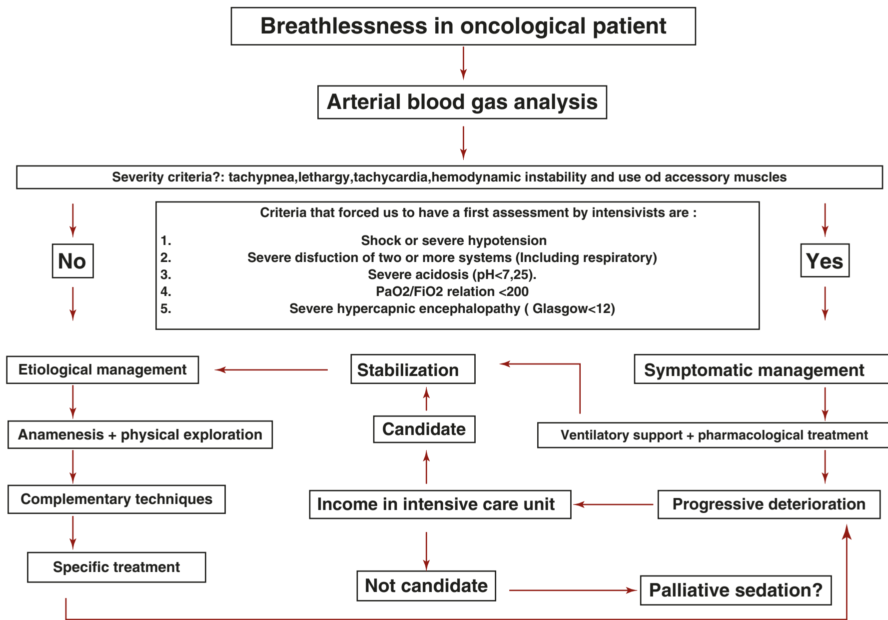

Fig. 2.2 Algorithm of management of dyspnea in oncological patient

symptoms, when opioids or other non-pharmacological measures have failed to control dyspnea. In fact, the combination of morphine with midazolam has shown good results in terminally ill patients.

Occasionally, it is erroneously believed that certain pharmacologic groups, such as bronchodilators, glucocorticoids, and diuretics, can be useful with regard to the control of dyspnea. This is only true in certain clinical scenarios (e.g., diuretics for pulmonary edema, corticoids in bronchospasm, etc.). For patients in the end of life that are not expected to benefit from any of these therapies, the use of palliative sedation provides relief of dyspnea; before considering a sedation, it is fundamental to ensure that the patient has a true indication, since this is an irreversible therapeutic intervention. Finally and to close this chapter, we show an algorithm that tries to summarize the management of dyspnea in this population (Fig. 2.2).

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Acute Respiratory Failure in Patients with Hematologic and Solid Malignancies: Global Approach

3

Sakshi Sethi and Stephen M. Pastores

Abbreviations

ARDS	Acute respiratory distress syndrome
ARF	Acute respiratory failure
BAL	Bronchoalveolar lavage
BMT	Bone marrow transplant
CMV	Cytomegalovirus
CT	Computerized tomography
DAH	Diffuse alveolar hemorrhage
EMG	Electromyography
FB-BAL	Fiber-optic bronchoscopy with bronchoalveolar lavage
HSCT	Hematopoietic stem cell transplantation
ICU	Intensive care unit
IVIg	Intravenous immunoglobulin
NIPPV	Noninvasive positive pressure ventilation
MV	Mechanical ventilation
PCP	*Pneumocystis jiroveci* pneumonia
PCR	Polymerase chain reaction
PE	Pulmonary embolism

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S. Sethi, M.D.
Department of Anesthesiology and Critical Care Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

S.M. Pastores, M.D., F.A.C.P., F.C.C.P., F.C.C. (✉)
Department of Anesthesiology and Critical Care Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Professor of Medicine and Anesthesiology, Weill Cornell Medical College, New York, NY, USA
e-mail: pastores@mskcc.org

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RSV	Respiratory syncytial virus
TRALI	Transfusion-related acute lung injury
VTE	Venous thromboembolism

3.1 Introduction

The incidence of all types of cancer is predicted to rise from 12.7 million new cases in 2008 to 22.2 million by 2030 [1]. Concomitantly, the last two decades have witnessed notable advances in the diagnosis and management of cancer patients including the use of high-dose chemotherapy, stem cell transplantation, targeted therapies, and immunotherapy. Although these strategies have significantly improved the overall and disease-free survival rates of patients with cancer, they have also resulted in increasing numbers of patients being admitted to the intensive care unit (ICU) for life-threatening toxic and infectious complications which are either cancer related or treatment associated.

Acute respiratory failure (ARF) is the leading cause for ICU admission in cancer patients and usually associated with high mortality rates especially in those requiring mechanical ventilation [2–4]. The incidence of ARF is about 5% in patients with solid tumors and up to 50% in those with hematological malignancies. Among hematopoietic stem cell transplant (HSCT) recipients requiring MV and ICU admission, the incidence of ARF ranges from 42 to 88% with an overall survival rate of approximately only 15% in those receiving MV [5].

The various causes of ARF in critically ill cancer patients are shown in Fig. 3.1. The most common causes include infections, cardiogenic and non-cardiogenic pulmonary edema (acute respiratory distress syndrome [ARDS]), antineoplastic therapy (chemotherapy, radiation therapy)-induced lung injury, malignancy-related medical disorders, and progression of underlying cancer.

3.2 Pulmonary Infections

Pulmonary infections are the leading cause of ARF, and the spectrum of possible responsible organisms depends on the underlying comorbidities (such as chronic lung disease, smoking history, cardiac failure, prolonged corticosteroid therapy), type of underlying malignancy, type of antineoplastic therapy, presence of neutropenia or defects in both cell-mediated and humoral immunity, frequent antibiotic exposure, and prophylactic treatments (Table 3.1).

3.2.1 Bacterial Pneumonia

Cancer patients with bacterial pneumonia tend to have atypical clinical features where fever is common but cough and sputum production are not. The chest radiograph may be normal or demonstrate diffuse interstitial infiltrates; the classic lobar