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Pulmonary Complications and Critical Care in Cancer Patients

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Introduction

Cancer refers to the condition where abnormal proliferation of cells occurs overriding the natural check of cell death.[1] As a normal physiological process, all cells of our body are programmed to die - called as apoptosis.[2] In cancer, the balance between cell proliferation and cell death is disrupted, resulting in uncontrolled division of cells.[3] Hence, apoptosis is an anti-cancer defense of body. In other words, carcinogenesis involves sequential genetic change that transforms normal cells to malignant cells. The cancer cells interfere with normal physiological functions and kill by invading various body organs vital for living. Cancer is a second leading cause of death worldwide, estimated to kill 9.6 million people in 2018.[4] Approximately, every sixth death is caused by cancer.[4] Globally, most common cancers are lung, breast, colorectal, prostate, skin and stomach cancers.

From the diagnosis to the treatment completion, cancer is a heart-rending experience for the patients as well as for their families. Cancer poses a great psychosocial impact including clinical stress, severe anxiety and depression on the patient, his/her spouse, offspring and other family members. The patient faces physical and mental health challenges during the treatment as well as throughout rest of the life, affecting quality of life.[5] Moreover, psychosocial stress adds to the disability of cancer patients. Therefore, the family and the treating clinicians should be aware of psychosocial problems associated with cancer. In this context, advanced psychosocial care including proper counseling, education, assurance of continued support and different forms of psychotherapy should be offered to the cancer patients and their families.[6]

In addition to its uncontrolled local disease, cancer accompanies with a number of complications along with its treatment and clinical course. These complications include neurological, skeletal, hematological, gastrointestinal tract and respiratory complications. The management of these complications differs from each other, and may require admission to intensive care unit (ICU). In this regard, acute life-threatening illnesses associated with cancer require ICU admission. Most often, the patients with leukemia, lymphoma and lung cancer are encountered in ICU.[7] The 5% and 15% of the patients with solid tumors and hematological malignancies require ICU admissions due to acute complications, respectively.[8] Similarly, 8% and 27% of the patients with lung cancer and other solid malignancies require ICU admissions, respectively.[8] Acute respiratory failure (ARF) occurs in 10-50% patients with oncologic malignancies.[9] ARF is the most common cause of admission to ICU. In this paper, we will review only pulmonary complications requiring ICU admission in the patients with cancers.

Search Strategy

An online search was conducted on the most-trusted medical database “PubMed” and “Google Scholar” using keywords such as “Pulmonary Complications”, “Cancer”, “Intensive Care Unit”, “ICU” or the combination of these words to collect articles related to our topic of interest. We read the articles thoroughly and carefully in order to write this review.

Literature Review

Pulmonary complications are common due to cancer and cancer treatment. For the way of explanation, pulmonary complications indicate a serious sequel of cancer or occur because of the therapies employed for the treatment of cancer. Pulmonary system is very sensitive to injuries caused by cancer therapy, resulting in fatal complications. These therapies may affect lung parenchyma, vasculature and pleural space.[9] Therefore, early detection of these complications and prompt treatment help improve prognosis and cancer-survival. Main reasons for the admission of cancer patients in ICU are acute respiratory failure (ARF), post-operative, infection and septic complications.[10,11]

Acute Respiratory Failure (ARF)

Acute respiratory failure (ARF) is a devastating condition in cancer patients where functions of lung or respiratory muscle pump are impaired, leading to high mortality.[12] About 15% of the patients with cancer suffer from ARF and require ICU admission where mortality rate of these patients is up to 50%.[13] Mortality is even higher in those who require mechanical ventilation.[12] Frequent causes of ARF include pulmonary infections, pulmonary edema (cardiogenic or non-cardiogenic), lung injury due to cancer therapy, venous thromboembolism (VTE), diffuse alveolar hemorrhage (DAH) and direct involvement of lung tissues by cancer.[14]

Pulmonary Infections (Pneumonia): Pneumonia refers to lung infection that is caused by organisms such as bacteria, viruses or fungi. The patients with cancer are at risk of developing pneumonia due to immunosuppression and hospital mortality remains high due to multi-resistant pathogens.[15] Studies reveal that bacterial pneumonias complicate 10% of cancer patients admitted in hospital, especially of those with hematological malignancies, where in, it poses risk of developing pneumonia in 30% cases. Similarly, 80% of cancer patients who receive hematopoietic stem cell transplantation (HSCT) encounter an

episode of pneumonia, causing death in 20% of them.[16] Obstructive pattern of lung function is a risk factor of pneumonia in cancer patients undergoing cytotoxic chemotherapy, resulting in incidence of pneumonia in 19% of cases.[17] The most common organisms causing bacteria in non-neutropenic phase include Streptococcus pneumoniae, Haemophilis influenzae and respiratory viruses while P. aeruginosa, Enterobacteraceae, S. pneumonia, P. aeruginosa are commonly encountered in neutropneic phase of cancer.[18] Additionally, Penicillin-resistant pneumococcus is also predominant in cancer patients.

The cancer patients are susceptible to bacterial pneumonias due to immune dysregulation, neutropenia, aspiration events, architectural damage to lungs (mucositis, impaired airway protection, etc.) and malnutrition.[19] Bacterial pneumonia increases morbidity and mortality in cancer patients. Neutropenia and cytotoxic therapies may result in life-threatening pneumonias.[16] Pneumonia in cancer patients accounts for 50% of the patients with septic shock.[20] Severe pneumonia requires ICU admission due to its high morbidity and mortality.[21] A number of severity scores such as Pneumonia Severity Index and the CURB65 score have been designed to assess the severity of community-acquired pneumonia (CAP); however, these scores are either limited value or underused, respectively.[22] On the other hand, delayed ICU admission is associated with high mortality. Therefore, prompt recognition of the severity of CAP and urgent transfer to ICU improve the clinical outcome.[22] Although neutopenia is an important risk factor for developing serious infections; however, it has no effect on mortality in the cancer patients.[23] Invasive ventilation and septic shock at the time of ICU admission are associated with high mortality.[23] It has also been studied that the patients with cancer and CAP have worse outcome as compared to those without cancer.[24] The reasons why the patients with cancer and CAP have worse outcome include immune dysfunction, prior hospitalizations and previous use of antibiotics, making the patients prone to infections with difficult pathogens. Intensive care with non-invasive mechanical ventilation, prompt intubation along with broad-spectrum antibiotics and nursing care are of prime importance in the clinical outcome.

Pulmonary Edema: Pulmonary edema refers to the excess fluid in the lung and lung spaces. There are two types of pulmonary edema: cardiogenic and non-cardiogenic. Cardiogenic pulmonary edema develops due to elevated pulmonary capillary pressure caused by left-sided heart failure. Non-cardiogenic pulmonary edema develops due to increased capillary permeability caused by endothelial and epithelial damage.[25] Acute pulmonary edema is an emergency and one of the common complications developed in the patients with cancer.[26] It can be cardiogenic or non-cardiogenic. Cardiogenic pulmonary edema in cancer patients may develop due to cardiomyopathy caused by certain drugs and radiotherapy used in cancer treatment. Similarly, non-cardiogenic pulmonary edema may develop due to acute reaction to the drugs (vinblatsine or mitomycin) or lung tissue damage due to cancer itself. Additionally, infections in cancer patients also cause non-cardiogenic pulmonary edema. Acute respiratory distress syndrome and capillary leak syndrome are acute and serious conditions affecting the lungs in cancer patients.[26]

The patients with cancer and pulmonary edema should be admitted to ICU to intubate as some studies report positive outcome.[27] However, these studies have not specified the characteristics of the patients who should be intubated. In this context, Zarogoulidis et al.,[27] suggested that BMI >25 kg/m^2 and low postoperative FEV1 can be used as predictive factors for the early admission to ICU. On the contrast, Griner.[28] recommends that appropriate treatment given to the patients with acute pulmonary edema in emergency room is sufficient, and only exceptionally ill patients should be admitted to ICU in order to make it cost-effective with short hospital stay. Other treatments of acute pulmonary edema include oxygen (if SpO2 <92%), nitrates, diuretics, morphine and inotropes.[29]

Venous Thromboemolism (VTE): VTE is a serious problem in the patients with cancer or those who undergo surgical procedures. In spite of its high mortality, many oncologists underestimate the severity of VTE in cancer patients.[30] In fact, cancer is an independent and major risk factor of VTE. It poses 6-7-fold greater risk of thrombosis as compared to general population without cancer, leading to increased morbidity and mortality.[30,31] VTE in the patients with cancer occurs due to Virchow's triad: cancer-induced hypercoagulability, endothelial damage and stasis.[32] Deep vein thrombosis (DVT) and pulmonary embolism (PE) are two major forms of VTE. Their risk increases when the patients are admitted to ICU post-operatively.[31] Risk of recurrent cancer-associated VTE and chemotherapy-associated VTE can be predicted by using Ottawa score and Khoranna score, respectively.[32]

Treatment of VTE in the patients with cancer is critical due to high risk of recurrent VTE and serious hemorrhagic events. Additionally, co-morbid conditions are a challenge for the management of VTE. Currently available treatment for cancer-associated VTE recommends low molecular weight heparin (LMWH) for cancer-associated VTE for 3-6 months, unfractionated heparin (UFH) for renal insufficiency, warfarin and fondaparinux heparin-induced thrombocytopenia (HIT).[32,33] It has been observed that LMWH are more effective than warfarin with similar profile of side effects. However, warfarin can be employed as an alternative where LMWH is contraindicated. Regarding VTE prophylaxis, all the hospitalized patients with reduced mobility and no contraindication should receive VTE prophylaxis.[34]

Diffuse Alveolar Hemorrhage (DAH): DAH is a life-threatening pulmonary complication in a number conditions including cancer. Risk factors of DAH include infections, low platelets and coagulopathy.[35] The mechanism of DAH is suggested to be due to disruption of the alveolar-capillary basement membrane caused by injury or inflammation.[36] Clinical presentation of DAH is non-specific including pyrexia, cough, hemoptysis, dyspnea and chest pain. However, DAH is a well-recognized complication of acute myeloid leukemia (AML) and the clinicians should be aware of this condition while dealing with AML. The patients with DAH requiring ICU admission may be dealt with supplemental oxygen therapy, mechanical ventilation, reversal of coagulopathy, plasmapharesis, platelet transfusion and hemodynamic support.[35]

Direct Invasion of Cancer: Lungs are also affected by direct effect of cancer, especially lung cancer. Lung cancer can invade adjacent tissues such as vascular bundle and chest wall. Additionally, pressure effect disturbs functional-anatomic integrity and plays important role in respiratory compromise.

Radiation Therapy Associated Pulmonary Complications: Radiation therapy is an important therapeutic modality used to treat cancer patients. It uses high dose of high-energy particles to damage cancer cells. Lung tissues (especially alveolar-capillary complex) are the most sensitive tissues to radiations. Along with damaging cancerous cells, radiation therapy damages the adjacent structures in the region of exposure. In fact, high-energy particles break strong chemical bonds releasing high reactive free radical species, which affect cellular components.[37] Radiation therapy can damage lungs in two phases: acute and late.[38] When a lung complication occurs before 6 months, it is called acute lung injury. Pneumonitis is an acute radiation-induced lung injury, which refers to inflammation of the lung tissue. Similarly, if a complication occurs after 6 months, it is called late complication. Fibrosis is a late radiation-induced lung injury that refers to scarring the lung tissues.

Treatment of radiation pneumonitis includes steroids, ACE inhibitors, pentoxyphylline and anti-oxidants.[38] Management of radiation fibrosis includes general supportive management (good nutrition, regular exercise, prophylactic vaccinations), clearing airway secretions (postural drainage, chest percussion, inhaled mannitol and hypertonic saline), anti-inflammatory agents (corticosteroids, antibiotics) and treatment of exacerbations.[38] Pneumonitis leads to respiratory failure warranting ICU admission where survival rate is improved.[39]

Chemotherapy-Related Pulmonary Complications: Chemotherapy may lead to direct or indirect potentially fatal complications.[40] It is a challenge to identify these complications early due to misinterpretation as other conditions like pulmonary edema, infections, and radiation pneumonitis. Chemotherapeutic agents may lead to cytotoxic pneumonitis, usual interstitial pneumonia (UIP) and drug-induced interstitial lung disease (DILD).[41] Primary management of chemotherapeutic pulmonary complications aims at suppressing inflammatory response and preventing continuing pulmonary fibrosis.[41]

Conclusion

Pulmonary complications in cancer patients are an additional challenge to healthcare system along with the management of primary malignancy. Most often, these pulmonary complications require critical care and admission to intensive care unit (ICU). Most common pulmonary complications among cancer patients are acute respiratory failure caused by various conditions such as pneumonia, pulmonary edema, VTE, DAH and direct invasion of lung tissues, and complications arising due to radiation therapy and chemotherapy. However, management of these complications in ICU is still controversial due to longer hospital stay and higher cost. Therefore, authors suggest ICU admissions only for those who are exceptionally ill. Moreover, there is need to evaluate outcome of ICU admissions for pulmonary complications in cancer patients in terms of short-term survival and overall mortality while considering the longer hospital stay and healthcare costs.

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