

Respiratory issues in cancer survivors patients: Mini-review

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Introduction

With the recent success of modern cancer therapy, cancer can be curable, and in cases where cure cannot be achieved, it can be treated as a chronic disease. As a result, there are now more than 15.5 million Americans with a history of cancer were alive on January 1, 2016. By January 1, 2026, this number is projected to reach 20.3 million [1]. These estimates do not include carcinoma in situ for any cancer except urinary bladder and do not include basal cell or squamous cell skin cancers. The respiratory effects of cancer therapy are critically important to the overall health of cancer survivors due to higher incidence of pulmonary disease compared with the general population. Because these conditions can result in a high degree of morbidity and mortality, understanding how to improve the prevention, recognition, and treatment of pulmonary disease is an important medical priority.

Cancer survivors are at increased risk for pulmonary disease that results from treatment with chemotherapy, immunotherapy and radiation therapy. This mini review paper will focus on the long-term respiratory and will also cover respiratory issues related to cancer therapy. These are reviewed below. Finally, practical recommendations will be made for certain principles that may help guide the optimal treatment of respiratory effects in cancer survivors.

Pneumonitis

Several chemotherapeutic agents are associated with interstitial pneumonitis, including bleomycin, cyclophosphamide, methotrexate, and carmustine. Of these, the pulmonary complications associated with bleomycin (an agent commonly used to treat Hodgkin lymphoma and testicular cancer) have been best characterized.

While this drug can cause a variety of insults, Bleomycin Interstitial Pneumonitis (BIP) is the most common. Depending on the definition used, BIP has been reported to occur in up to 46 percent of patients [2]. BIP is of particular relevance to the long-term care of cancer survivors, given its potential progression to pulmonary fibrosis and associated increased mortality. For example, a study of 38,907 survivors of testicular cancer treated

with bleomycin in the past revealed an increased standardized mortality ratio of 2.53 (95% CI 1.26-4.53) for respiratory diseases alone [3]. Late onset BIP typically develops more than six months after treatment [4,5] presenting as a nonproductive cough, dyspnea, tachypnea, fever, and cyanosis. Radiographic imaging demonstrates variable findings but can show bilateral bibasilar infiltrate [2]. Patients with BIP tend to respond to corticosteroids [4,6].

Pneumonitis can also occur with radiation therapy and typically occurs at least one to three months after completion of radiation therapy for lung, breast, esophageal cancers and bone metastases, Hodgkin and non-Hodgkin lymphoma, or total body irradiation for leukemia. The incidence and extent of radiation damage depends on the volume of lung irradiated, total radiation dose, and radiation fractions [7]. Again, common symptoms include dyspnea, hypoxia, nonproductive cough, and fever. Radiographic imaging tends to show changes confined to the outlines of radiation fields [7]. Steroids can be helpful and patients can have complete resolution of symptoms after six to eight weeks of treatment. Like BIP, however, radiation pneumonitis can progress to fibrosis, making this particularly relevant to the care of long-term survivors.

Immune-related pneumonitis

Immune-checkpoint inhibitor therapy has emerged as a promising treatment option for advanced cancers [8-10]. Two PD-1 inhibitors have been approved by the U.S. Food and Drug Administration (FDA) for the clinical cancer treatment, including nivolumab for advanced melanoma, NSCLC, and RCC, and pembrolizumab for melanoma and NSCLC. A combination therapy using nivolumab and ipilimumab, a CTLA-4 inhibitor, has also been approved as a treatment for advanced melanoma [11,12]. Given the evidence for clinical efficacy in a wide spectrum of tumor types, PD-1 immune-checkpoint inhibitor therapy as monotherapy or in combination is projected to be increasingly used by oncologists. Immune-checkpoint blockade by PD-1 inhibitors is associated with unique toxicities, termed immune-related adverse events (irAEs), which can involve different organs throughout the body [13-15]. Among the irAEs, pneumonitis is a relatively rare, but clinically serious and potentially life-

threatening toxicity which might affect the quality of life specially those patients who achieve a durable response. Time from initiation of therapy to the development of pneumonitis had a wide range (0.5- 11.5 months), indicating an importance of careful observation and follow-up for signs and symptoms (i.e. cough and dyspnea) of pneumonitis throughout treatment. Shorter time to onset of pneumonitis in lung cancer compared to melanoma and lymphoma may be due to a higher pulmonary tumor burden among lung cancer patients, which can result in an earlier onset of respiratory symptoms. Immune-related pneumonitis showed a spectrum of radiographic patterns, which were associated with toxicity grades. The incidence of immune-related mild/moderated pneumonitis is increased in patients who has previously received lung radiation therapy following the administration of durvalumab (PDL-1 inhibitor) as it was demonstrated in the Pacific trial [16].

Radiographic pattern of pneumonitis has a wide spectrum where the most frequently are the ground-glass opacities followed by cryptogenic organizing pneumonia, non-specific interstitial pneumonia, acute interstitial pneumonia/acute respiratory distress syndrome and hypersensitivity pneumonitis [17]. Most cases were responsive to corticosteroids and around one-third of the patients are able to restart therapy, though a few patients experienced recurrent pneumonitis during retreatment. These observations emphasize the importance of increased awareness of the entity for the early diagnosis and treatment.

Fibrosis

Pulmonary fibrosis is a dreaded complication of certain chemotherapies, including bleomycin, busulfan, and carmustine, and radiation treatment. In a small study of 17 children who received carmustine to treat brain neoplasms, 25-year follow-up revealed that nine (53 percent) died of pulmonary fibrosis. Of the eight survivors, follow-up was available on seven patients, who all showed signs of upper zone pulmonary fibrosis [18]. Radiation-induced pulmonary fibrosis develops at least 6 to 24 months after exposure to radiation, with patients presenting with progressive dyspnea and cough. In some cases, fibrosis is observed on imaging alone and patients are asymptomatic [19]. Steroids typically are associated with little benefit. The Childhood Cancer Survivor Study demonstrated that patients exposed to chest radiation were 4.3 times more likely than their siblings to have pulmonary fibrosis five years postdiagnosis. Chest radiation was also associated with a 3.5 percent cumulative incidence of pulmonary fibrosis 20 years post-diagnosis [20].

Bronchiolitis obliterans syndrome

Pulmonary complications, specifically Bronchiolitis Obliterans Syndrome (BOS) and idiopathic pneumonia syndrome, are a significant source of morbidity and mortality in the Hematopoietic Stem Cell Transplantation (HSCT) population. Among 438 HSCT patients surviving more than three months, the incidence of late noninfectious pulmonary complications was 10 percent and the five-year survival rate of these patients was significantly lower compared with patients without pulmonary disease (34 versus 65 percent) [21]. BOS is a complication seen after allogeneic

HSCT and is observed in the presence of chronic graft-versus-host disease. This syndrome causes airflow obstruction secondary to progressive circumferential fibrosis with eventual scarring of terminal bronchioles [22]. It typically occurs within the first two years after transplant but can occur later, at four or five years. In 2005, the following National Institute of Health (NIH) diagnostic criteria were proposed: forced expiratory volume in one second (FEV₁) <75 percent predicted; FEV₁ /forced vital capacity (FVC) ratio <0.7; evidence of air trapping, small airway thickening, or bronchiectasis on high-resolution computed tomography (HRCT) or residual volume (RV) >120 percent of predicted normal; and absence of respiratory tract infection or pathologic confirmation [23]. Using these criteria for BOS, a single center study of 1145 patients revealed a prevalence of 5.5 percent in transplanted patients and 14 percent in patients with chronic graft-versus-host disease [23]. However, International Bone Marrow Transplant registry data on 6275 adult patients with leukemia treated with allogeneic HSCT reported an incidence of only 1.7 percent using prior diagnostic criteria [25].

In its early stages, patients are rarely symptomatic or have nonspecific symptoms of mild dyspnea on exertion or non-productive cough. However, as the disease progresses, patients suffer from significant dyspnea on exertion, persistent nonproductive cough, and decreased exercise tolerance. If BOS worsens, patients eventually develop significant hypoxia and become oxygen dependent, and alongside this an increased risk for pulmonary infections [26]. Diagnostic evaluation includes pulmonary function tests, HRCT, echocardiography to assess pulmonary artery pressures, infectious work-up, complete graft-versus-host evaluation, bronchoalveolar lavage, and tissue biopsy. Steroids are the mainstay of treatment, although their use has not been evaluated in large clinical trials. Long-term survival is poor. Among 2859 bone marrow transplant patients, five-year survival of patients with BOS was 10 versus 40 percent in patients without BOS. In patients with BOS who responded to initial treatment with steroids, 79 percent survived at five years versus 13 percent if there was no response [27]. A 2011 consensus statement originating from the Consensus Conference on Clinical Practice in Chronic GVHD recommended routine pulmonary function testing screening in asymptomatic patients at 3, 6, 9, 12, 18 and 24 months after allogeneic stem cell transplantation and then annually [26].

Idiopathic pneumonia syndrome

Idiopathic pneumonia syndrome (IPS) includes a spectrum of noninfectious lung injury that carries a high mortality rate. In 2010, IPS was defined as an "idiopathic syndrome of pneumopathy after HSCT, with evidence of widespread alveolar injury and in which infectious etiologies and cardiac dysfunction, acute renal failure or iatrogenic fluid overload have been excluded" [28]. The median onset is considered to be six to seven weeks but more recently has been shown to occur as early as 19 days post-transplant (28), with an incidence estimated to be on the order of 12 percent. Patients present with dyspnea, nonproductive cough, and hypoxemia, with non-lobar infiltrates are seen on radiographs [29]. The syndrome typically leads to rapid respiratory failure and

death. In 2003, Fukada et al reported a cumulative incidence of IPS of 2.2 percent in patients treated with non-myeloablative versus 8.4 percent in patients who underwent conventional conditioning prior to allogeneic HSCT ($p = 0.003$) and a mortality rate of 75 percent [30]. Etanercept, a TNF-alpha binding protein, has shown some benefit in the treatment of these patients [31,32].

Secondary lung cancer

RT to the chest increases the risk of subsequent lung cancer. Among 64,782 breast cancer survivors who had surgery, at 10 to 14 years and >15 years from their initial diagnosis, patients who received radiation were at a significantly higher relative risk of lung cancer than those who did not (relative risk [RR] 1.62, 95% CI 1.05-2.54 and RR 1.49, 95% CI 1.05-2.14, respectively) [33]. Other populations who receive chest RT appear to also be at risk; in another study of survivors of Hodgkin lymphoma, those treated with chest RT had a relative risk of 2.7 to 7.0 of developing lung cancer [34].

Monitoring pulmonary function and follow-up

For patients suspected of having symptoms attributable to pulmonary toxicity, pulmonary function tests can be used to aid in the diagnosis of subclinical, asymptomatic disease. Despite the potential discrepancy between pulmonary function tests and overt clinical symptoms, early identification for pulmonary disease is important given it is a significant cause of mortality in adult survivors. In a Childhood Cancer Survivor Study which included 20,483 five-year survivors of childhood cancer, the cumulative mortality at 30 years from diagnosis was 18.1 percent (95% CI, 17.3-18.9) and survivors were 8.8 times more likely to die from a pulmonary cause [35].

Summary

In a study of 1713 survivors of childhood cancer, 65.2 percent (95% CI 60.4-69.8) had abnormal pulmonary function tests with the highest prevalence in those treated with lung radiation (74.4 percent [95% CI 69.1-79.2]), bleomycin (73.5 percent [95% CI 61.9-82.9]), and thoracotomy (53.2 [95% CI 44.1-62.0]) [36]. In another study that included 220 five-year childhood cancer survivors who received potentially pulmonary toxic chemotherapy, 44 percent had abnormal pulmonary function tests at a median follow-up of 18 years. Restrictive lung disease and decreased carbon monoxide diffusion capacity were the most common abnormality [37].

Long-term follow-up with spirometry and questionnaires of 1049 testicular cancer survivors showed that 8 percent had restrictive lung disease. In this study, patients treated with cumulative cisplatin dose greater than 850 mg and patients treated with cisplatin and pulmonary surgery had increased odds of developing restrictive lung disease compared with patients treated with surgery alone. Interestingly, of the patients diagnosed with restrictive lung disease, only 9.5 percent had self-reported dyspnea and 7.5 percent had prevalent asthma [38].

Pulmonary effects of chemotherapy, immune-check point inhibitors and chest radiation can have an insidious onset

and devastating consequences. Providers should be aware of conditions that can present months or years after cancer treatment and are associated with increased bad quality of life and mortality.

Diagnostic evaluation can include pulmonary function tests, echocardiograms to assess pulmonary pressures, and chest radiographic imaging in patients who have been exposed to pulmonary toxic chemotherapy or chest radiation. Cancer survivors who continue to smoke tobacco should be counseled to discontinue tobacco use. Several studies have shown smoking increases the risk of a second malignancy [39,40].

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