Malignancy After Lung Transplantation: A Literature Review

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Abstract

Background: Over the past two decades there have been significant improvements in the quality of life and long-term survival of lung transplant patients. Nevertheless, it has been noted that a number of malignancies have developed in lung-transplant recipients pursuant to lung transplantations. It is therefore important for medical practitioners, other health care workers, and the public to be aware and well informed about the types of malignancies that develop after lung transplantation.

Aim: To review the literature on malignancies that develop pursuant to lung transplantations.

Literature Review: A number of malignancies have been reported following lung transplantation and these include:
- Post-transplantation lymphoproliferative disorders;
- Skin cancers – non-melanotic skin cancers (squamous cell carcinomas; basal cell carcinomas); Kaposi’s sarcoma; Bronchogenic carcinomas; lymphomas; Carcinomas of colon; Adenocarcinomas of stomach; Adenocarcinomas of prostate; Renal carcinomas; Laryngeal cancers; Seminomas; Basaliomas; Carcinoma-in-situ of the cervix; Bladder cancer; Breast cancer; Hepato-biliary carcinoma; Anal cancer; Other miscellaneous malignancies.

A multitude of predisposition factors have been postulated to be responsible for the development of the various malignancies that develop after lung transplantation. It has been stipulated that the aetiology of post-transplantation malignancies involve a combination of:
* Impaired renal function
* Impaired immune activity against viruses
* DNA damage and disruption of DNA repair mechanisms
* Promotion of tumour progression by cytokine up-regulation and transforming growth factor 1, interleukin IL-10 and vascular endothelial growth factor.

Conclusion and Recommendations: A number of malignancies develop after lung-transplantation in view of this careful and regular follow-up assessment of all lung-transplant recipients is required for the early detection and management of cancer. Pre-disposing factors for the development of malignancy should be avoided / minimised in the lung-transplant recipient.

Key words: Malignancy; Lung-transplant; recipient; skin cancer; lymphoproliferative disorders, Kaposi’s sarcoma; bronchogenic carcinoma; genetic; predisposition.

Introduction

First described in 1986, lung transplantation is typically offered to patients with end stage pulmonary disease and who have a life expectancy of less than 18 months. The majority of lung transplantations are for chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF) and cystic fibrosis (CF). The median survival for adult lung recipients has been reported as five and a half years[1].

In the past 20 years, there have been significant improvements in quality of life and long term survival after lung transplantation due to developments in surgical techniques, perioperative management and immunosuppressive therapy such as tacrolimus and mycophenolic acid [2]. Common complications post-transplantation of the lung include graft failure, infection, bronchiolitis and rejection. However, transplantation patients are at high risk of developing infections and malignancies due to prolonged exposure to immunosuppressive drugs [3-5], yet insufficient immunosuppression results in graft loss.

There are a wide-spectrum of malignancies that can develop after transplantation of a solid organ and those commonly after lung transplantation include post-transplantation lymphoproliferative disorder (PTLD), skin cancer and bronchogenic carcinoma.

In this paper we have reviewed the literature on the development of malignancy after lung transplantation and the role of immunosuppressant.

Review

Incidence

Dantal [6] in 2007 stated that an immunosuppressed transplant patients has a three to five time higher risk of developing cancer than a non transplant patient. Around 82% of transplant patients develop non-melanotic skin cancers (NMSC), just over a tenth develop PTLD and 6% develop Kaposi’s sarcoma (KS).
[7-9]; these are the most common malignancies in transplant patients. Other malignancies include uterine carcinoma-in-situ, hepatobiliary carcinoma, anogenital carcinoma and gastrointestinal (GI) tumours. Interesting data from the United States[10] has illustrated the incidence of the following malignancies in transplant patients in comparison to the general population (of the same age):

* Two fold incidence: lung, colon, breast and prostate cancer
* Three fold incidence: bladder and testicular cancer
* 15 fold incidence: renal cancer
* 20 fold incidence: NMSC.

Data from the Registry of the International Society for Heart and Lung Transplantation [1] (ISHLT) in 2011 showed that causes of death post-transplantation at 30 days include graft failure (27%) and non-cytomegalovirus (CMV) infection (20%). Causes of death at 10 years after lung transplantation include:

* Bronchiolitis (19%)
* Infection (18%)
* Graft failure (16%)
* Lymphoma (4%)
* Other malignancy (11%).

The registry states that 3.5% of surviving lung transplant patients develop at least one malignancy a year after transplantation (lymphoma), 13% at five years and 27% at ten years after transplantation. At five and ten years, the commonest malignancy seen was of the skin.

Aetiology

Our natural immune response deals with our daily exposure to carcinogens or mutagens. However, the inadequate immune response in patients on immunosuppressive therapy can account for the development of post transplant malignancies. Common risk factors in the development of malignancies include [11]:

* Increasing age
* Cigarette smoking
* Exposure to ultraviolet (UV) light
* Sun exposure
* Latent oncogenic viruses
* Previous exposure to carcinogens
* Analgesic abuse.

Genetic predisposition or predisposition to certain malignancies in some countries also can play a role, for example, liver tumours in South East Asia and GI tumours in Japan[12]. It has been suggested that the aetiology of post-transplantation malignancies involves a combination of the following[13]:

* Impaired immune surveillance of neoplastic cells
* Impaired immune activity against viruses
* DNA damage and disruption of DNA repair mechanisms
* Promote tumour progression by cytokine up-regulation and transforming growth factor 1, interleukin IL-10 and vascular endothelial growth factor.

It has been acknowledged for many decades by Penn[14-15] that the incidence of malignant tumours in transplant patients was caused by the administration of immunosuppressants. Traditionally, solid organ transplant recipients would receive cyclosporine, azathioprine and prednisolone as maintenance therapy. However, due to the increased risk of rejection and bronchiolitis post lung transplantation, positive results from heart, kidney and liver transplantations have meant lung transplant recipients now often receive tacrolimus or mycophenolic acid. The Registry reports no consensus regarding maintenance immuosuppression agents, but the most frequently used calcineurin inhibitor was tacrolimus at one year (82%) and five years (75%) after transplantation[1]. The most frequently used purine synthesis antagonist at both one and five years was mycophenolic acid[1]. It has been reported that the percentage of recipients with acute rejection in the first year was highest with cyclosporine and lowest with tacrolimus[1].

* Data[16] revealed that the following are important factors in the role between immunosuppression and post-transplantation malignancies:
  * Length of exposure to immunosuppressive agents
  * Intensity of therapy
  * More intense immunosuppression (once malignancy has developed) causing more aggressive tumour progression in terms of growth and spread
  * Immunosuppressive agents impair cancer surveillance and facilitate the action of oncogenic viruses
  * The cancer-promoting effect of calcineurin inhibitors, independently of depressed immunosurveillance.

Post-transplantation lymphoproliferative disorder

This condition, PTLD, is a well known complication of solid organ transplantation and is characterised by lymphoid proliferation: polymorphic or monomorphic, polyclonal or monoclonal, atypical lymphocytic infiltrates or lymphoma. It is also strongly linked to immunosuppression, CMV and Epstein-Barr virus (EBV).

The incidence of PTLD varies in transplant recipients and is typically higher in liver, lung and heart transplant patients, especially in the first year after surgery[17-18]. In lung transplant recipients, it has been reported that the incidence of PTLD can vary from 2.5% to 8%[19-22].
Paraanjhoti and associates[19] identified PTLD in 30 of 494 (6.1%) lung or heart-lung transplant patients which presented most frequently in the thorax and allograft one year after surgery. The authors concluded that PTLD confined to the allograft carried a better prognosis than those at other sites in the body, such as the GI tract in later years.

Regarding risk factors, it has been shown that PTLD in lung recipients is more common in:
* Older patients with COPD[22]
* EBV negative (pre-transplantation) recipients[24]. These patients should be treated with lower levels of immunosuppression.

In patients with heart or heart-lung transplants, no correlation of development of PTLD was found with different immunosuppression regimens. These consisted of azathioprine, prednisone, cyclosporine, OKT3 induction, tacrolimus and mycophenolate mofetil.

A young recipient age, high rejection frequency and high-dose cyclosporine immunosuppression were significantly associated with PTLD development. The prevalence of PTLD in 58 long-term survivors of lung-transplantation was unexpectedly high at 15%[23].

Regarding treatment, it has been shown that PTLD in solid organ or allogeneic bone marrow transplantation can be successfully treated with surgical resection or chemotherapy without compromising the graft[20].

Rituximab has been shown to be successful in treatment of PTLD in lung transplant recipients[22]. Kremer et al [25] reported an incidence of 4.8% of PTLD after lung transplantation but found that the incidence has decreased over the years due to modern immunosuppression. Many patients presented with fatigue, pain and weight loss. The current pathogenesis model of PTLD after transplantation suggests T-cell suppression causes the proliferation of viruses which triggers B-cell proliferation and malignancy[26]. Results show that PTLD is more common in patients induced with anti-thymocyte globulin and the leukocyte-depleting monoclonal antibody OKT3 after lung transplantation[25,27-29]. With the introduction of a new induction agent, daclizumab, the incidence of PTLD has decreased. Regarding the role of maintenance immunosuppression and PTLD, literature seems to be unclear due to variety of agents used[25,29-31].

Skin cancer
Non-melanotic skin cancer is a common malignancy after solid organ transplantation. Up to 90% of post-transplantation NMSC consist of squamous cell carcinoma (SCC) and basal cell carcinoma (BCC). The incidence of SCC is 65-250 times greater in transplant patients than the general public. For post-transplantation BCC, the incidence is up to 10 times greater than the general population. Risk factors for NMSC after transplantation include lifelong immunosuppression, UV exposure (together with fair skin), Human Papilloma Virus (HPV) 8, HPV 19 and genetic factors (mutations of p53 and proto-oncogenes)[9]. Cancers such as SCC and BCC have been linked to older age, male sex, actinic keratosis (premalignant) and cigarette smoking[32].

The incidence of NMSC increases as the duration of immunosuppression increases. It has been suggested that cyclosporine free sirolimus based immunotherapy is effective as a study showed that transplanted patients using this agent developed no skin malignancies[33]. Cyclosporine induces cytokine production which promotes carcinogenesis and increase the risk of skin cancers and PTLD[34]. Also, azathioprine increases the risk of SCC[34].

As mentioned earlier, the Registry of the ISHLT reports that the most common malignancy seen in patients at five and ten years after lung transplantation is that of the skin. The incidence of skin cancers after lung transplantation is 1% at one year, 8.4% at five years and 18% at 10 years[1]. Parada et al [34] reported that in 59 lung transplant patients, seven developed malignancies (11.8%) of which five were skin cancers.

* Bronchogenic carcinoma
* Lung cancer can arise in lung transplant recipients from three different origins[35]:
  * The donor organ
  * Be misdiagnosed pre-operatively
  * De novo after transplantation.

Several factors increase susceptibility to cancer in transplant recipients, as mentioned above but those specific to the development of lung cancer have discussed much in literature. Host influences in a lung transplant patient are likely to include tobacco use or certain underlying disease processes, such as IPF. Immunosuppression is related to the development of non-Hodgkin’s lymphoma and KS in organ transplant recipients. However, data has not proven that this extends to the development of epithelial cell tumours such as lung cancer[4].

Collins and and associates[36] followed 2,168 single lung recipients and found that 24 (1%) developed cancer in the native lung. The frequencies were 2% and 4% in patients with emphysema and IPF respectively. Most manifested as nodules or masses on chest x-radiographs but more nodules were picked up on computed tomography (CT) imaging. Studies [2, 37-39] have reported similar results and an incidence of 2.4% to 4.3% mostly in the native lung after single or bilateral lung transplantation. The time interval...
between single/bilateral lung transplantation and diagnosis of lung cancer has been reported by several studies to range between 4 months and 9 years[36,38,40] but commonly between three and five years.

Risk factors for developing lung cancer after lung transplantation include:

* In the native lung[38]
* COPD/IPF patients[38]
* Smokers[38]
* Increasing age[40]
* Single lung transplantation[40].

Also, cancer in the native lung after single lung transplantation is more common than lung cancer in a bilateral lung recipient. Dickinson et al [40] reported an incidence of lung cancer (non small cell) in the native lung in just less than 7% of 131 single lung recipients and 0% in 131 bilateral lung recipients. Similarly, a study reported that 8.9% of single lung recipients and 1% of bilateral lung recipients developed lung cancer, with just under 10% of single lung recipients (with emphysema or IPF) developing it in their native lung[37].

Literature suggests that bronchogenic carcinoma of the non small cell origin can develop after single or bilateral lung transplantation. Now Picard et al[41] reported an interesting case of small cell lung carcinoma in a 25 year old female bilateral lung recipient. She had a background history of CF and was a non smoker. The cancer was of recipient origin as there was a gender mismatch between donor and recipient and illustrates the chimerism of the bronchial epithelium after lung transplantation.

Other malignancies

As mentioned earlier, KS is a well known post-transplantation malignancy and in particular in recipients of renal, liver, heart or bone allografts. It has been reported that 6% of transplant recipients develop KS[5-7]. Kaposi's sarcoma is a tumour caused by the Human Herpes Virus-8 and is a systemic disease that can present with or without internal involvement. Four different subtypes have been described:

* Classic KS affecting middle aged men of Mediterranean and Jewish descent
* African endemic KS
* Kaposi's sarcoma in immunosuppressed patients (iatrogenic)
* Acquired immune deficiency syndrome (AIDS)-related KS.

However, there does not seem to be much literature regarding KS after lung transplantation. A study reported that three of a group of 121 (2.5%) lung or heart-lung transplant recipients (between 1992 and 2004) developed KS[5]. Sachsenberg-Studer et al[42] presented an interesting case study surrounding the development of KS of both the skin and lung graft in a Human Immunodeficiency Virus (HIV) negative patient who underwent a single lung transplantation for emphysema. Also, a case of bronchial KS (in trachea and native lung) six months after a single lung transplantation for end stage COPD has been reported[43].

Other malignancies reported in the literature after lung transplantation include the following:

* Colon cancer[2,5,44]
* Gastric adenocarcinoma[2,34]
* Transitional cell carcinoma of the bladder[5,44]
* Prostatic adenocarcinoma[34,44]
* Renal cancer[44]
* Laryngeal cancer[2]
* Seminoma[45]
* Basalioma[45]
* Carcinoma-in-situ of the cervix[45].

Conclusion

Malignancy is a well known complication of solid organ transplantation. Common malignancies after lung transplantation include PTLD, skin cancers and bronchogenic carcinoma. Lymphomas most commonly develop in the early years after lung transplantation and skin cancers later. Various mechanisms have been proposed regarding the aetiology of post-transplantation malignancies but lifelong immunosuppressants are thought to play a big role.

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