Transplantation Reviews xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Transplantation Reviews

journal homepage: www.elsevier.com/locate/trre

Review article

Etiology of increased cancer incidence after solid organ transplantation

Sergio A. Acuna [a,b,c,d,*]

[a] Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Canada
[b] Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Canada
[c] Department of Surgery, St. Michael's Hospital, Toronto, Canada
[d] Division of General Surgery, Department of Surgery, University of Toronto, Toronto, Canada

ARTICLE INFO

Available online xxxx

Keywords:
Solid organ transplantation
Cancer incidence
Immunosuppression
Risk factors

ABSTRACT

Over the past decades, there has been an encouraging increase in survival after solid organ transplantation. However, with longer life spans, more transplant recipients are at risk of dying with functioning grafts from illnesses such as cancer and cardiovascular conditions. Malignancy has emerged as an important cause of death in transplant recipients and is expected to become the leading cause of death in transplanted patients within the next decade. While it is known that solid organ transplant recipients have a three to five-fold increased risk of developing cancer compared with the general population, the mechanisms that lead to the observed excess risk in transplant recipients are less clear. This review explores the etiology of the increased cancer incidence in solid organ transplant including the effect of immunosuppressants on immunosurveillance and activation of oncogenic viruses, and carcinogenic effects of these medications; the role of chronic stimulation of the immune system on the development of cancer; and the impact of pre-existing cancer risk factors and factors related to end-stage organ disease on the cancer excess incidence in solid organ transplant recipients.

Contents

1. Introduction

In the early days of transplantation, a high incidence of lymphomas and skin malignancies in solid organ transplant recipients (SOTR) was noted by Drs. Thomas Starzl and Israel Penn [1,2]. Original accounts estimated that the cancer incidence was approximately 80 times greater than in the general population in a comparable age range [1]. Subsequent population-based studies found a three to five-fold increased risk of neoplasia among SOTR compared with the general population [3–10]. Transplant patients are at elevated risk for a wide range of solid-organ tumor types, with marked excess incidence of non-melanoma skin cancer (NMSC) and non-Hodgkin's lymphoma (NHL). Excess incidence has also been observed for cancer of the vulva and

* Corresponding author at: Division of General Surgery, Department of Surgery, University of Toronto, Sunnybrook Hospital, 2075 Bayview Ave, Suite H-317, Toronto, Ontario M4N 3M5, Canada.
E-mail address: sergio.acuna@utoronto.ca.

https://doi.org/10.1016/j.trre.2018.07.001
0955-470X/

vagina, anal canal, oral cavity, kidney and to a lesser extent the oesophagus, stomach, large bowel, urinary bladder, lung, and thyroid gland [3–9]. A study employing competing risk methodology to estimate the absolute risk of developing a malignancy after transplantation in US solid organ recipients observed a cumulative incidence of cancer of 4.4% within 5 years from transplantation [11]. Moreover, the increasing cumulative incidence of cancer was observed during the same period that the hazard of death, graft failure, or retransplantation declined [11].

The etiology of the excess risk of developing cancer after transplantation is likely multifactorial (Fig. 1). The high incidence post-transplant *de novo* malignancy has been attributed to decreased immunosurveillance, activation of oncogenic viruses, chronic stimulation of the immune system, carcinogenic effects of immunosuppressants, pre-existing cancer risk factors, and factors related to end-stage organ disease, or dialysis in the case of kidney recipients. Cancer incidence has been shown to differ by transplanted organ. The overall excess cancer incidence observed is the greatest for lung transplant recipients [8,12]. The incidence of NHL has been shown to be greater in cardiothoracic transplant recipients [8,12]. However, population-based studies have demonstrated that the risk of NHL and lip cancer did not significantly differ by organ type after adjustment by type and dose of immunosuppression [13,14]. Similarly, the excess incidence of NMSC and cancer of the lip is much less in liver recipients than other transplant recipients. Liver recipients have also been shown to not be at excess risk for cancer of the anal canal. As these malignancies have an underlying viral association, the lower incidence may reflect lower doses of maintenance immunosuppression, and avoidance of induction agents in liver transplant protocols [12]. Moreover, dose-dependent association between cyclosporine A (CsA) levels and incidence of cancer after transplantation have been observed in a randomized controlled trial (RCT) [15]. Immunosuppressant medications can induce neoplastic transformation through direct carcinogenesis or secondary to the induction of immunosuppression, which can lead to infection and proliferation of oncogenic viruses and reduce immunosurveillance functions of the immune system. Moreover, some diseases for which transplantation is undertaken may be associated with malignancy or may be a marker of exposure to potential carcinogens (i.e. smoking) [12].

2. Immunosuppression and immunosurveillance

The study of the interactions between the immune system and cancer has been closely linked to that of allograft rejection [16]. Initial observations of an immune response capable of recognizing and destroying transplanted tumours in animal experiments soon were demonstrated to be related to allograft rejection rather than tumor-specific cytotoxicity [16]. However, the discovery of tumor-specific antigens to which mice could be immunized against and the demonstration of a higher incidence of chemically-induced and spontaneous tumours in immunodeficient compared with immunocompetent mice led to the formal proposal of the immune surveillance hypothesis by Sir Macfarlane Burnet and Lewis Thomas in 1957 [17]. However, due to the inability to confirm the immune surveillance theory, the higher incidence of tumours in immunodeficient mice was assumed to be solely related to greater susceptibility of immune-compromised host to infectious agents [16].

Several key findings in the 1990's renewed interest in cancer immunosurveillance, specifically the demonstration that endogenous production of interferon (IFN)-γ protected against growth of transformed tumor cells and formation of both chemically induced and spontaneous tumours [18], and the observation that mice lacking perforin, a component of cytolytic granules of cytotoxic T cells and NK cells important in lymphocyte-dependent killing, were more prone to developing chemically-induced tumours [19].

Further advancement in the cancer immunology field led to the establishment of cancer immunosurveillance not as an isolated mechanism but rather as part of a larger process denominated cancer immune-editing with a dual role in cancer [16]. While the immune system can suppress tumor growth by destroying cancer cells or inhibiting their outgrowth (elimination phase), it can also promote tumor progression by selecting for tumor cells that are more fit to survive in an immunocompetent host (equilibrium phase) or by establishing conditions within the tumor microenvironment that facilitate tumor outgrowth (escape phase) [20].

The cancer immune-editing process encompasses three sequential phases (Fig. 2). The elimination phase corresponds to the initial phase of the neoplastic process where newly generated tumor cells are identified and eliminated by natural killer (NK) cells and CD8+ cytotoxic T cells. If this phase is successful, the host remains free of cancer. However, if some cell variants are not destroyed, the neoplastic process enters the equilibrium phase. During this phase, tumor outgrowth is prevented by immunologic mechanisms. However, because of the constant immune selection process and greater tumor heterogeneity due to genetic instability, new tumor variants with no immunogenic potential emerge. These tumor cells are insensitive to immune-mediated tumor growth restrictions and further induce an immunosuppressive state in the tumor microenvironment.

In the transplant setting, understanding the relationship between immunosuppression and cancer immune-editing is complicated as SOTR receive multidrug treatment regimens that act on different parts of the immune system and through different mechanisms [21]. Research to clarify the interactions between pharmacological immunosuppression and cancer immune response has only recently begun. CD8+ cytotoxic T cells, and more specifically, central memory T cells (T_{CM}), have been shown to play a key role in the cancer immunosurveillance (i.e. elimination phase) [22,23]. CD8+ cytotoxic T cells are also involved in allograph rejection, but this is mainly mediated by CD8+ effector memory T cells (T_{EM}) [24]. Immunosuppressants used in transplantation such as inhibitors of mammalian target of Rapamycin (mTOR) can induce a shift toward a central memory phenotype [25]. This promotion of CD8+ T_{CM} cells has also been shown to enhance immune responses against viral antigens [25]. In addition, mTOR inhibitors upregulate CD4+ type 1 T-helper (T_{H1}) cell hallmark T-box transcription factor T-bet [26]. T-bet appears to be essential for tumor-suppressive activities and optimal antitumor responses by regulating the cross-talk of innate and adaptive immune cells [27]. In contrast, common immunosuppressants such as

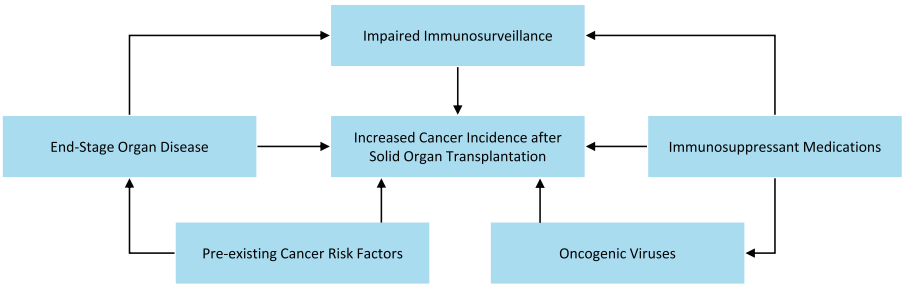

Fig. 1. Etiology of increased cancer incidence after transplantation.

Please cite this article as: Acuna SA, Etiology of increased cancer incidence after solid organ transplantation, Transplantation Reviews (2018), https://doi.org/10.1016/j.trre.2018.07.001