Malignancy after Renal transplantation: A review of the literature

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Abstract

Background: Renal transplant recipients have superior over-all survival and a better quality of life in comparison with patients with end-stage renal disease who remain on chronic long-term dialysis. Nevertheless, various types of malignancies have been reported in a number of renal transplant recipients pursuant to their renal transplantations

Aims: To review the literature on malignancies in renal transplant recipients after their transplant operations

Results: Literature review has revealed that:

- Patient survival after renal transplantation has improved considerably over the past 30 years. However, life expectancy remains far worse than in the general population.
- Cardiovascular disease is the leading cause of death pursuant to renal transplantation but post-transplant malignancies are becoming increasingly common and are fast becoming a major burden affecting long-term survival.
- In comparison with the general population, several types of malignancies occur more commonly in transplant recipients and are more often aggressive and often associated with worse prognosis.
- In renal transplant recipients, skin cancers and lymphomas are among the prevalent malignancies.
- A number of risk factors contribute to the incidence of cancer including both conventional risk factors and those specific to transplant recipients.
- In transplant recipients, commonly known factors such as oncogenic viruses, exposure to ultraviolet light, total sun burden, previous exposure to carcinogens, cigarette smoking, advanced age, geographic location, and genetic predisposition, immune-suppression, increasing age, and a history of malignancy are risk factors to the transplant recipient population.

Conclusions: Knowledge about the increased incidence and aetiological causes of malignancy in the transplant recipient has led to the adoption of the following measures:

- Regular screening for cancer being available post-transplantation to all renal transplant recipients in order to enable early intervention when a cancer is detected.
- Attempts being made to balance the risks of graft rejection and the development of cancer by means of modulating immune-suppressive therapy in renal transplant recipients.
- Malignancies are being managed by means of specific therapies for particular tumor types and by means of strategies including immune-suppression reduction, immune-suppression withdrawal or conversion to alternative immune-suppressive regimens.

Introduction

Some authors [1] [2] have stated that patients with end-stage renal disease who undergo renal transplantation have superior over-all survival and a better quality of life than patients on long-term dialysis. Reports from a variety of studies have reported that renal transplantation is associated with a lower risk of mortality in comparison with staying on the transplantation waiting list on dialysis [3], [4], [5]. This finding has been confirmed with regard to a number of different situations including:

- Different age groups [6]
- Patients of different ethnicities [6]
- Diabetic patients [6]
- Patients on long-term dialysis.

Kidney transplantation is the treatment of choice in patients with end-stage renal disease who initially are managed by dialysis until a suitable donor of kidney for transplantation is found.

The use of new immuno-suppressive drugs over the past few decades has led to improvement in outcome of renal transplant patients. The incidence of acute graft rejection in renal transplant patients has reduced following the introduction of drugs such as mycophenolate and tacrolimus [8], [9]. Despite the fact that the reduction in acute graft rejection has resulted in improved survival rates [8], [9], chronic graft rejection is still a frequently encountered complication. Solid-organ transplant recipients who receive chronic...
treatment by means of immune-suppressive agents prevent allograft rejection, nevertheless, have a higher risk of developing malignancy in comparison with the general population, malignancy is the third most common cause of death after cardiovascular events and infection among transplant recipients at all time points after transplantation [11], [12], & [13].

In this paper, we have reviewed the literature on malignancies developing following renal transplantation focussing on the influence of immune-suppressive agents on the development of malignancies or the prevention of malignancies.

Literature Review

Aetiology: The aetiology of post-transplantation malignancy appears to be multi-factorial and perhaps involves a combination of events as follows;

- Impaired immune activity against viruses
- Impaired immune-surveillance of neoplastic cells
- DNA damage and disruption of DNA repair mechanisms
- The up-regulation of cytokines that can promote tumour progression for instance, transforming growth factor β1, interleukin [IL]-10, and vascular endothelial growth factor. [12]

All the aforementioned events occur during long-term immune-suppressive therapy after renal transplantation. [12]

Solid –organ transplantation has been reported to be associated with the ensuing increases in cancer incidence:

As early as in the 1970’s an increase in the incidence of malignant tumours in transplant recipients was recognized and this was attributed to the administration of immune-suppressive medication. [14] [15]

The clinician, in the early days of transplantation, experienced fulminant acute graft rejection episodes and severe infections; malignancies after renal transplantation represented only a minor occurrence. These days as a result of longer graft survival and older donors as well as recipients, and with the introduction of more potent immunosuppressive therapy, malignancy now represents a major burden in transplantation medication. Birkeland and associates [16] as well as Peto [17] reported that the over-all incidence of malignancy after renal transplantation is 3 to 5 times higher in comparison with the general population.

Nevertheless, Morath and associates [18] stated that an increased frequency is not found for all types of cancer. Reports from a number of sources including the Cincinnati transplant Tumor Registry have suggested that the most frequent types of tumors are post-transplantation lymphoproliferative disorders (PTLD) and squamous cell carcinoma (lip, vulva, skin).[19 ], [20].

Malignancies occurring in a renal transplant recipient after transplantation can develop in three different ways as follows:

- De novo occurrence in the recipient
- Recurrent malignancy in the recipient
- Transmission of malignancy from the donor.

A number of factors have been thought to play a role in the pathogenesis of post renal transplant malignancies.

The occurrence of De Novo malignancy in the recipient

A number of conditions have been attributed to the development of De Novo malignancy in a renal transplant recipient including: immune-suppression and malignant transformation; conventional risk factors; Genetic factors; chronic viral infections; geographic differences.

Immono-suppression and malignant transformation

Skin cancer and lympho-proliferative disease are the two most common types of malignancies seen in renal transplant recipients. Literature review indicates that malignancies of the lympho-proliferative system occur mostly within the first three years following renal transplantation. The high over-all risk of malignancy in heavily immune-suppressed patients is primarily due to the development of non Hodgkin lymphoma (NHL). It has been stated that the introduction of new and more potent immunosuppressive regimens is associated with an increased incidence of cancer following renal transplantation [21]. However, this statement has not been supported by solid epidemiological evidence. Conflicting reports exist on whether or not the introduction of cyclosporine was followed by a higher frequency of malignant tumours [22] & [23].

Penn and First [24] also reported that malignancies are more frequently encountered in patients on triple drug regimens that include cyclosporine, azathioprine, and corticosteroids.

Opelz and Henderson [ 10] stated that there is a bit of dispute regarding the suggestion that the development of lymphomas is particularly increased in those patients who receive polyclonal or monoclonal
antibodies for induction or rescue therapy and this is true for recipients of both cardiac and renal allografts.

Cherikh and associates [25] reported that: in an analysis of the United Network of Organ Sharing (UNOS), the risk of malignancy was particularly high in patients who received a combination of monoclonal antibodies, tacrolimus, and mycophenolate mofetil; and in patients who received this immunotherapy regimen, the over-all risk of any type of cancer in comparison with the matched background population was increased by a factor of 5.11, and the risk of PTLD was higher by a factor of 27.2.

A number of authors have stated that the postulate that the action of immunosuppressive drugs is the aetiological cause for the increased incidence of tumours in transplant recipients is affirmed by the observation that the patients in addition develop tumours if they receive treatment for conditions other than transplantation, for example, systemic lupus erythematosus (SLE), rheumatoid arthritis, or dermatomyositis; an increased incidence of lymphoproliferative disease in these patients has been attributed to the administration of immunosuppressive agents, such as cyclophosphamide, methotrexate, and azathioprine [26, 27, & 28].

It has been stated that the relationship between the intensity of immuno-suppression and increased incidence of tumours has been shown convincingly for skin cancer [18]. Dreno [29] stated that exposure to sunlight which is a risk factor for squamous cell carcinoma and basal cell carcinoma is also a risk factor for transplant individuals. Ramsay and associates [30] as well as Fortina and associates [31] stipulated that the duration and intensity of immuno-suppression are additional risk factors.

Berg and Otley [32] stated that the predisposition to squamous cell carcinoma may perhaps also be related to the high prevalence of human papilloma virus (HPV) in transplant patients; presumably as a result of immuno-suppression, it has been found in about 90% of allograft recipients.

E6 and E7 which are viral proteins of human papilloma virus (HPV) inhibit the tumour suppressor gene p53 and are considered to be involved in the induction of carcinoma in this high risk population [malignancy in renal transplant]. Furthermore, the exposure of the skin to ultra-violet radiation induces DNA mutations by the formation of thymidine dimers which lead to inactivation of the tumour suppressor p53. [18] The end product of failure of such mutations is thought to result in malignancy [18].

Farag and associates [33] stated that:

- The relationship between tumorigenesis and immune-suppression is not completely understood.
- Natural killer cells play an important role in the host’s defence against malignancy.

Seaman and associates [34] stated that depletion of natural killer cells (NK-1.1) in mice increased the implantation and growth of B16 melanoma cells or CT 38 colon carcinoma cells.

Rushfeldt and associates [35] stated that after the injection of colonic carcinoma cells into the superior mesenteric vein of syngeneic mice, injection of natural killer cells together with interferon –v reduced the tumour cell burden in the liver. Herzyk and associates [36] reported that an association with increased tumour colonization was observed following administration of anti-T-cell antibodies; for example, anti-Thy 1.2 or anti-asialo CM-1. But this was not true for all immune-modulatory antibodies. As an example, anti-CD4 monoclonal antibody (kelixmab) did not interfere with the immune-response against malignant cells in mice.

Guba and associates [37] stated that it is believed that the newly introduced immunosuppressive agent Sirolimus (Rapamycin) combines immunosuppressive action with anti-tumour effects.

Morath and associates [18] are of the opinion that the aforementioned clinical and experimental observations are compatible with the concept that the increased frequency of malignancies in recipients of allografts results mainly from immuno-suppression. They also stated that this simple concept does not fully explain that the excess tumour incidence in kidney recipients is restricted to certain malignancies, for example, skin tumours and lymphoma. In addition it appeared to Morath and associates [18] that immune-suppression alone is not sufficient for the development of tumour, and that additional determining risk factors including patient’s genetic background, viral co-infection, or exposure to sun apparently play a role.

Conventional Risk Factors: Dampanich and associates [38] stated that common risk factors related to the development of post transplantation malignancy include: cigarette smoking and advanced age. Other reported risk factors include analgesic abuse as stated by Pommer and associates. [39] In addition Kliem and associates [40] stated that in patients with a history of phenacetin abuse the risk of uro-epithelial carcinoma is quite high and this observation led to the postulate that nephroureterectomy should be performed prior to the renal transplantation.

Genetic Factors: Dampanich and associates [38] found in their study that patients who had an invasive
cancer before transplantation had a much higher risk (RR 2.38) of developing a second invasive carcinoma de novo after transplantation. Goldfarb and associates [41] stated that:

- Some rare primary renal diseases (especially von Hippel-Lindau disease) are associated with an intrinsically higher risk of developing renal cell carcinoma with aggressive course.
- When such patients receive a renal allograft, then the frequency of renal cell carcinoma increases.

It has been stated that the risk of carcinoma is also markedly increased in patients with Wiskott-Aldrich syndrome or Drash syndrome [18]. Cleper and associates [42] as well as Fischer and associates [43] stated that in transplant recipients with these rare syndromes, an excessive frequency of lymphoma and Wilms’ tumour was noted.

Morath and associates [18] stated that the postulate that genetic predisposition has a role to play in the genesis of post-transplant malignancies is supported by the observation that patients with malignancies after transplantation quite often have more than one type of tumour. Gomez and associates [44] reported patients with as many as three different types of tumours.

Morath associates [18] stated that the most common secondary malignancy in patients with two malignancies is a skin tumour and that in a retrospective study by London and associates [45] skin tumours were found in 10 of 70 recipients of renal allograft who had other types of malignancies.

Chronic Viral Infections: Some viral infections predispose recipients of transplants to specific varieties of malignancies. Lye [46] stated that Epstein-Barr virus (EBV) is frequently associated with the development of lymphoma, and human herpes virus 8 (HHV 8) is frequently associated with the development of Kaposi’s sarcoma.

Bird and associates [47] reported that 98% of cases of with post-transplant lympho-proliferative disorders are associated with latent Epstein-Barr virus infection via T cell-mediated suppression of viral growth. Schmidtko and associates [48] stated that:

- T-cell surveillance is impaired by cyclosporine, and it is even more disturbed by antibodies directed against T cell, for example, OKT3 or ATG.
- Results of in vitro studies showed that co-incubation of Epstein-Barr Virus-infected B cells with OKT3 or ATG led to increased B cell proliferation and immortalization and such a mechanism is likely in life.
- They observed Epstein-Barr virus associated post-transplantation –lympho-proliferative disorders after renal transplantation in primates, and this was especially prominent in animals receiving an aggressive immunosuppressive conditioning regimen. This finding was consistent with a study by Opelz and associates [10] of transplanted patients in which a higher rate of non Hodgkin lymphoma was found after the administration of anti-lymphocyte antibodies.

Cathomas and associates [49] found an association of Kaposi’s sarcoma and HHV 8 infection in 18 renal transplant recipients. They also noted that these patients had received monoclonal or polyclonal antibodies as induction or rescue therapy for steroid resistant rejection. [49]

Harwood and associates, [50] reported the association between varying types of papilloma virus and carcinomas of skin, cervix, ano-genitalia and penis.

Nickelett and associates [51] stated that Polyoma virus is a double-stranded DNA virus which induces acute interstitial nephritis in recipients of renal transplants. Ichaso and associates [52] as well as Benjamin [53] also stated that Polyoma virus causes acute renal dysfunction and is also tumourigenic by transforming cells by the action of middle T antigen.

Mechanism of virus-induced tumour formation

Thomson [54] as well as Hay and associates [55] stated that for any virus to induce uncontrolled cell proliferation in vivo, at least three processes must take place as follows:

- The virus must uncouple the mechanisms controlling progress of the cell cycle and cell division.
- The virus must prevent the host cell from undergoing apoptosis.
- The proliferating cell, bearing viral-derived antigens on its surface must escape the attention of the host immune system.

Scaffidi and associates [56] stated that:

- The escape from apoptosis is a requirement for sustained growth after transformation of the host cell by oncogenic viruses.
- A class of proteins [FLIPs (FADD I like Interleukin I B converting enzyme-like protease Inhibited proteins)], interfere with the initiation of apoptosis at the level of death receptors.

Muller and associates [57] stated that:

A number of FLIPs are encoded by class v? Herpes viruses, for example, herpes virus Saimiri (HVS) or HHV 8, so-called viral FLIPs (vFLIPs) inhibit apoptosis through several apoptosis-reducing receptors (CD95, TNF-RI, TRAMP/DR3, and TRAIL-RI) that presumably share common signalling pathways.

Morath and associates [18] stated that:
All viruses encoding vFLIPs can transform cells in vitro and they are associated with tumours in susceptible hosts.


HHV 8 is associated with Kaposi’s sarcoma and multi-centric Castleman disease.

Hanahan and associates [58] stated that another important pathway for virus-induced malignancy is the interference of p53 tumour suppressor gene. Morath and associates [18] stated that:

- P53 induces cell cycle arrest or apoptosis in response to DNA damage.
- Small DNA viruses use distinct mechanisms to counter p53. They either, bind directly to p53 and inhibit p53-mediated transcriptional activation, or they promote the degradation of p53 via ubiquitin pathway.

Transmission of Malignancy from the Donor

Even though transmission of a tumour by means of (micro) metastases of undiagnosed malignancy in a donor to a recipient is rare, this possibility should be considered in the differential diagnosis of malignancy after transplantation. Myron Kaufman and associates [59] reported on data from the Organ Procurement and Transplantation Network / UNOS. They reported that:

- In 108,062 transplant recipients a total of 21 donor-related malignancies were found.
- Fifteen tumours were donor-transmitted (malignancies which existed in the donor at the time of transplantation).
- Six tumours were donor-derived (de novo tumours that develop in transplanted haematogenous or lymphoid cells of the donor).

Some authors [6], [20], and [60] also stated that Donor-derived tumours have been reported in allografts obtained from donors with bronchial carcinoma, carcinoma of breast, and malignant melanoma. In some patients, cessation of immune-suppression had led to rejection of the donor-derived malignancy without further therapy. In majority of patients, however, specific anti-tumour therapy was necessary (i.e. surgery, chemotherapy, radiation, to induce remission).

Clinical Manifestations: The origin of the cancer which develops after renal transplantation determines the clinical characteristics of the malignancies [61]. The time of presentation also depends on the nature of the malignancy. However, one study found that the average time to cancer development was 3 years after transplantation. [61] Mao and associates [62] stated that it seems that recipients of solid-organ transplant experience worse prognosis than the general population. Miso and associates [62] also stated that at the time of diagnosis, cancers seem to be more aggressive in solid-organ transplant recipients than in the general population.

Skin Cancers: Adami and associates, [63] and de Fijter [64] stated that non-melanoma skin cancers are the most common cancer type pursuant to solid organ renal transplantation.

Some authors [6] & [64] have stipulated that basal cell carcinoma and squamous cell carcinoma constitute >90% of all non-melanoma skin cancers which occur in solid-organ transplant recipients. Other authors [65] & [66], stated that non-melanoma skin cancers occur an average of 8 years following renal transplantation in recipients aged less than 40 years, and more quickly, after 3 years, in recipients older than 60 years. Nevertheless, perhaps this data might only be a function of the follow-up period of the particular studies.

Squamous cell carcinoma is the most common non-melanoma skin cancer occurring following solid-organ transplantation. Miao [62] reported that:

- The risk is 100 times greater in transplant recipients than in the general population.
- Both tumour types on the whole are generally more aggressive in transplant recipients in comparison with the general population and the risk of recurrence after treatment is on the whole higher.
- Lesions tend to develop at a younger age in transplant recipients and are more likely to develop in multiple sites.

Urwin and associates [67] stipulated that the most pertinent risk determining factor for the development of non-melanoma skin cancer in renal transplant recipients is previous exposure to ultraviolet radiation.

Furthermore, Pedotti and associates [68] stated that the development of squamous cell carcinoma tends to be associated with the following:

- Premalignant keratosis.
- Bowen’s disease (squamous cell carcinoma in situ).
- And / or kerato-acanthosis.

Urwin and associates [67] developed a predictive index which could be used to enable targeted screening for non-melanoma skin cancer in renal transplant recipients and these include:

- Age
- Exposure to outdoor ultraviolet radiation
- Living in a hot climate
- Pre-transplantation non-melanoma skin cancer
- Sun burn during childhood
- Skin type.
Melanoma

Vajdic and associates [69] stated that:

- The risk of developing melanoma is 3.6 times greater in renal transplant patients than in the general population.
- The risk of the development of melanoma in renal transplant recipients is positively linked with increasing age at transplantation; and with use of depleting anti-lymphocyte antibodies.
- On the contrary, female sex, non-Gaussian race, and increasing time since the transplantation were inversely associated with the risk of the development of melanoma.

Even though renal transplant recipients are said to be at increased risk of developing melanoma, some authors [70] & [71] found that the outcomes of melanoma in transplant recipients were not different to in the general population. Nevertheless, Miao and associates [62] reported that outcomes may be worse in transplant recipients than in the general population, in view of the fact that transplant recipients are more likely to have more advanced malignant melanoma at the time of diagnosis.

Kaposi’s sarcoma

Birkeland and associates [16] stated that the incidence of Kaposi’s sarcoma is much higher in renal transplant recipients than in the general population. Campistol and associates [72] stated that:

- Kaposi’s sarcoma is caused by herpes virus 8
- Kaposi’s sarcoma is three times more common in male renal transplant recipients than in the female renal transplant recipients
- Most cases of post-transplantation Kaposi’s sarcoma occur in individuals of Mediterranean, Jewish, Arabic, Caribbean, or African descent; a finding which perhaps corresponds with the distribution of human herpes virus 8.

Moosa [73] stated that:

- The choice of immunosuppressive therapy can affect the risk of post-transplantation Kaposi’s sarcoma in that calcineurin inhibitors are associated with a higher risk of the development of Kaposi’s sarcoma in comparison with other immunosuppressive therapies.
- Typically, Kaposi’s sarcoma manifests as angiomatous lesions predominantly affecting the legs and causing lymphoedema; Lesions can also occur on mucosal surfaces, gastro-intestinal tract, lungs, and lymphoid tissue.
- Kaposi’s sarcoma is quite often limited to the skin in transplant recipients. However, visceral involvement which tends to be associated with a worse outcome, occurs in 10% of patients.
- The incidence of visceral involvement tends to be lower in renal transplant recipients in comparison with heart and liver transplant recipients, perhaps because immune-suppression regimens involving calcineurin inhibitors are less intensive in renal transplantation.

Contrary to the statement of Moosa in 2005 [73], Frances and associates [74] in 2009 reported a multi-centre study in a large cohort of renal transplant patients. They found out that the presence of pre-existing or acquired human herpes virus 8 infection did not have any effect on graft or patient survival, which in their opinion would suggest that patients who are seropositive for human herpes virus 8 should not automatically be excluded from transplantation.

Lymphoproliferative disorders

Pascual [75] defined post-transplantation lymphoproliferative disorder (PTLD) as a heterogeneous group of diseases which are characterized by abnormal lymphoid proliferation occurring after organ transplantation. Pascual stated that even though PTLD usually manifests as host-derived B-cell neoplasia, T-cell and donor-derived lymphomas have also been described.

Kasiske and associates [76] stated that PTLD is more common among transplant recipients than B-cell, and T-cell lymphoproliferative disorders are in the general population as well as patients who are on the waiting list for transplantation.

Caillard and associates [77] studied 66,159 adult kidney transplant recipients and found that malignant lymphoid proliferation developed in 1,169 patients (1.8%) over an average follow-up duration of 10 years. Of these patients 70% were diagnosed with non-Hodgkin lymphoma, 14% with malignant melanoma, 11% with lymphoid leukemia, and 5% with Hodgkin lymphoma. Caillard and associates [77] stated that:

- Despite the fact that the average time to the development of PTLD is 32 months after transplantation, the incidence of the development of lymphoma is highest during the first year after transplantation, when the risk of primary viral infection is highest and the level of immune-suppression is greatest.
- Non-Hodgkin lymphoma notably has a more aggressive clinical course in renal transplant recipients than in the general population, with the involvement of extra-nodal areas and poorer prognosis.

Koukourgianni and associates [78], stated that in paediatric renal transplant recipients, the reported incidence of PTLD approaches 5% at 10 years following transplantation.
Miscellaneous Cancers

Merkel's cell carcinoma

Berg and associates [32] as well as Penn and First [79], stated that Merkel's cell carcinoma is an aggressive neuro-endocrine skin cancer which has been described in solid-organ transplant recipients. Berg and associates [32], as well as Penn and First [79] reported the following characteristics of Merkel's cell carcinoma:

- This cancer predominantly affects upper extremities, head and neck.
- It has a more aggressive prognosis in transplant recipients than in the general population.
- The mean time of occurrence of Merkel's cell carcinoma following transplantation has been reported to be about 7 years.
- The mean survival after diagnosis is 18 months (range 0-135 months).

Squamous cell carcinoma of the eye

Vadjic and associates [80] stipulated that:

- The incidence of squamous cell carcinoma of the eye is 20-fold higher in renal transplant recipients in comparison with the general population.
- The incidence of squamous cell carcinoma of the eye is also increased in individuals with HIV which would suggest that this type of cancer (squamous cell carcinoma of eye) has an origin related to immune deficiency.
- Nevertheless, this malignancy has been found to be associated with exposure to sun.

Cancers involving the ano-genital region

A number of authors [63], [81], & [82] have stated that:

- The incidence of cancers involving the ano-genital region is 100-fold higher among renal transplant recipients in comparison with the general population.
- The distribution of such cancer involves multiple sites including the anus, peri-anal skin, and external genitalia of both sexes.
- This cancer manifests as maculopapular lesions.

Lung cancer

Some authors [83], [84], & [85] have stated that the incidence of lung cancer is higher in heart or lung transplant recipients who smoke than in non-smoking lung or heart transplant recipients and prophylactic globulins that are used for induction therapy have also been associated with lung cancer in solid-organ transplant recipients.

Management of the Allograft Recipient with a Pre-existing Malignancy

When a patient with end-stage renal failure is put on the waiting list for renal transplantation, the question does arise as to whether a history of malignant disease should be a contra-indication for transplantation. Penn [86] reported a retrospective study which comprised of 913 recipients of renal allograft with 939 pre-existing cancer, showing that quite often the nephrologist would need to deal with this problem in this present day's aging dialysis population.

Morath and associates [18] stated that:

- There is consensus that a two-year waiting period should be interposed between the successful treatment of a cancer and transplantation.
- A waiting period is not required for the following tumours: (a) incidentally diagnosed renal cell carcinoma, (b) any type of in-situ carcinoma, (c) or basal cell carcinoma of the skin.
- In view of a high likelihood of recurrence even beyond the second year after treatment, a waiting period of more than two years is advisable in patients with a history of (a) malignant melanoma, (b) breast cancer, and (c) colo-rectal- carcinoma.

Penn [87] addressed the issue of recurrence in a retrospective study comprising of 1297 renal allografts recipients with a history of malignancy. Penn [88] reported that:

- The frequency of recurrence after transplantation was 21% for tumours diagnosed and treated before transplantation.
- For tumours diagnosed and treated after transplantation the frequency of recurrence was 33%.
- With regard to tumours diagnosed and treated before transplantation, the frequency of recurrence following transplantation was highest for breast cancer, symptomatic renal cell cancer, sarcoma, bladder cancer, and multiple myeloma.

Management of the Allograft Recipient with De Novo Malignancy after transplantation

Morath and associates [18] stated that:

- In the event of a patient developing a malignancy de novo following transplantation, it would be asked whether it is useful to reduce or stop immune-suppression.
- The underlying idea of reducing or stopping immune-suppression is that this move might allow rejection of the malignancy by the recipient’s recovering immune system.
- If immuno-suppression is stopped early following transplantation, graft monitoring at short intervals would be necessary, or else, fulminating rejection may be discovered too late with the potential result of graft rupture; in such a situation removal of graft would be advisable.

Penn, [88] reported successful reduction or cessation of immunosuppression in transplanted patients who developed non Hodgkin lymphoma and kaposi's...
sarcota. Despite this, Boye and associates [89] reported the rate of death remained high in patients with post-transplant lymphoma.

Some authors [Boye and associates [89], Fischer and associates [90], as well as Stephan and associates [new 91] reported that therapeutic strategies targeting B cells [61] [89], including local or systemic administration of specific anti-CD24-, anti-CD21-, and anti-CD20- (rituximab) B cell antibodies, were successful with a follow-up of several months [90] & [91].

Pirsch and associates [92] reported successful antiviral treatment with acyclovir, valacyclovir, or ganciclovir in Epstein-Barr virus-induced lymphoproliferative disease. In patients who do not respond to these treatments, or in severe disease, Cotti and Remuzzi [94] have recommended a treatment regimen including cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP).

Morath and associates [18] recommended that:

- Transplant recipients with pre-malignant skin lesions should be referred to a dermatologist for active treatment and close follow-up.
- Skin cancers should be completely removed.
- Secondary prevention should include the use of topical or systemic retinoids in patients with actinic keratoses and squamous-cell carcinoma and reduction of immunosuppression when possible.

Al- Sulaiman and Khader [94] stated that:

- Post-transplant Kaposi's sarcoma is the tumour with the highest relative risk in comparison with the background population.
- The clinical course quite often is aggressive, with a mortality rate of 34% within three years of the initial diagnosis.
- Involvement of visceral organs is an indicator of severe disease.
- Aggressive forms of gastro-intestinal involvement may be diagnosed during endoscopy.

Cotti and associates [93] stated that reduction of immunosuppression leads to complete remission in 30% of the patients; localized lesions may be treated surgically or by local radiation.

Screening of the Allograft Recipient for Malignancy

Kasiske and associates [95] have advised that regular screening for the detection of tumour when a patient is considered for renal transplantation and also especially after transplantation.

Morath and associates [18] recommended that

- As a result of the rising age of patients on the waiting list for renal transplantation and because of the increasing time that patients spend on the waiting list to undergo renal transplantation, the risk that malignancy will escape detection is increased so that potential transplant recipients with pre-existing tumours would receive transplants.
  - Clinical history, physical examination, and attention to symptoms suggestive of organ involvement by post-transplantation-lympho-proliferative disorders should be performed every three months in the first year after transplantation and at least yearly thereafter
  - Periodic inspection of the entire skin (to detect skin tumours) by a dermatologist is mandatory (at least at yearly intervals).
  - In the case of high-risk patients, for example, those who have been previously diagnosed with squamous cell carcinoma, more frequent controls are indicated (at least every six months).
  - Primary prevention of skin cancer should include avoidance of exposure to sun, use of protective clothing, use of effective sunscreen by the patient as directed by the European Best Practice guidelines [96]

According to Seukeran and associates [97], compliance is a universal problem in that only 54% of the transplant recipients remembered that they had received any advice concerning cancer prevention, and only thirty per cent of patients knew why extra precautions against cancer were necessary.

Other recommendations made by various authors include:

- Yearly gynaecological examinations are mandatory to exclude vulvar, perineal, and uterine malignancies. In women who have not had hysterectomy, trans-vaginal ultrasonography is recommended. [18]
- Ultrasoundographic examinations of the recipient's kidneys should be performed at least at yearly intervals in view of the fact that multi-cystic transformation of contracted kidneys in patients with primary renal disease is a pre-cancerous condition. [18]
- Urological examination is indicated in patients with a history of analgesic nephropathy who develop microscopic haematuria. [18]
- Another high-risk group who should have urological examinations includes those patients who received cyclophosphamide for the treatment of vasculitis, especially in those patients where the cumulative dose exceeds 20 grams. [98]
- Patients who have been treated with azathioprine for more than 10 years should have urological examinations / screening. [99]
- Periodic screening of faeces for occult blood is advisable in view of the fact that colonic carcinoma is more frequent after renal transplantation. [100]
- Patients with a history of uretero-sigmoidostomy should undergo colonoscopy at least 10 years after renal transplantation because of the risk of late-colonic carcinoma. [100]
- In the case of other solid organ cancers (prostate, breast), guidelines published for screening and
prevention of solid organ cancers in the general population should be strictly applied to transplant patients. [18]

Conclusions

Malignancy is a well noted common cause of death following renal transplantation. Associations have been established linking many of the immunosuppressive drugs currently in use with cancer pursuant to transplantation.

Attempts are being made through research to develop strategies that are aimed at the prevention of tumour development as well as treatment of tumour. Patients on waiting list for renal transplantation are being screened for the detection of cancer and transplant recipients are also being screened for cancer. Attempts are being made to minimize doses of immunosuppressive drugs that are potential risk factors for the development of cancer as preventive strategy in transplant recipients; interest is also growing in the potential antioncogenic properties and inherent immunosuppressive peculiarities of mTOR inhibitors.

The ensuing points regarding malignancy after renal transplantation should be noted.

- Malignancy is the 3rd most common cause of death following renal transplantation.
- Common malignancies that have been encountered in renal transplant recipients include: skin cancer; melanoma; Kapoeli’s sarcoma; post-transplantation lymphoproliferative disorders.
- Some of the factors that have been linked with the development of cancer in renal transplant recipients include: impaired immune surveillance due to immune-suppression; carcinogenic factors; genetic pre-disposition to cancer; presence of certain viral infections.
- Regular screening for cancer should be available post-transplantation to all renal transplant recipients in order to enable early intervention when a cancer is detected.
- Attempts should be made to balance the risks of graft rejection and the development of cancer by means of modulating immune-suppressive therapy in renal transplant recipients.
- It is important that malignancies should be managed by means of specific therapies for particular tumour types and by means of strategies including immune-suppression reduction, immune-suppression withdrawal or conversion to alternative immune-suppressive regimens.

References

34. Seaman W E, Steisenger M, Eriksson E, Koo G C. Depletion of natural killer cells in mice by monoclonal antibody to NK-1.1 Reduction in host defence against malignancy without loss of cellular or humoral immunity. J Immunol 1987; 138: 4539 – 4544
52. Ichaso N, Dilworth S M. Cell transformation by the middle T antigen of polyoma virus. Oncogeny 2001; 20: 7908 – 7916
58. Hanahan D, Weinberg R A. The hallmarks of cancer Cell 2000; 100: 57 - 70
64. de Fijter J W. Use of proliferation signal inhibitors in non-melanoma skin cancer following transplantation. Nephrol. Dial. Transplant. 2007; 22 (Suppl. 1): i23 – i26


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