Incidence of Neoplastic Disease in Cardiac Allograft Recipients

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Incidence of neoplastic disease represents a serious complication after heart transplantation. In this review, the authors discuss the incidence, causes, and types of tumors in cardiac allograft recipients. Prevention and tumor monitoring for early treatment are highlighted.
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Heart transplantation (HTx) represents an accepted therapeutic option in the treatment of end-stage heart failure. As cardiac transplantation has evolved, postoperative survival results have improved. However, malignant disorders in survivors are a serious complication after HTx.

The immune system uses its unique ability to discriminate between autologous constituents (self) and foreign antigens (nonself) and, when activated, generates a specific response.[1] In the late 1960s, thanks to the insights of Paul Ehrlich a century earlier, Burnet[2] formulated a general hypothesis that assigned to the immune system a central role in the destruction not only of microorganisms and cells infected with a virus, or after allogenic transplantation, but also toward those cells that, due to somatic or hereditary mutations, may represent a potential risk of transformation into cancer cells.

Although tumors are derived from self-tissues, the process of malignant transformation may be accompanied by the expression of tumor antigens that, if recognized as foreign by the immune system, can trigger an immune response against cancer cells, with the purpose of eradicating the tumor. This theoretical

role played by the immune system, known as *immunosurveillance*, is based on two main assumptions: 1) that cancer cells have new antigens on their surface that are absent on normal cells; and 2) that the immune system activated by these antigens is able to control the spread of the tumor.[3] The growth of a neoplasm should be considered an evasion of this monitoring system. Escape from the immune system's protective effects against tumors can take place through various complex mechanisms, but it can be attributed to two main factors: 1) the failure or decreased immunogenicity of tumor cells; and 2) the immune system having an impaired ability to react to tumor antigens. Different mechanisms may contribute to the increased risk of malignancy in transplanted patients (Table 1).

Immunosuppression and Transplantation

If we exclude the historical stages of total body irradiation, and the use of azathioprine prescribed in combination with steroids (in use since the early 1960s), it is with the introduction into clinical practice of cyclosporin A, a cyclic peptide derived from *Trichoderma polysporum*, that the face of immunosuppressive therapy has completely changed.

Since the 1980s, there has been a progressive improvement in immunosuppression therapy with a reduction of cyclosporine dosages. First was a transition from a dual therapy (cyclosporine and corticosteroids) to a triple therapy with the addition of azathioprine. Subsequently, the use of globulins or antithymocyte antibodies was introduced, and then the use of mycophenolate in place of azathioprine and tacrolimus instead of cyclosporine.[4] In recent years, two other pharmacological agents belonging to a new family of immunosuppressants called mammalian target of rapamycin inhibitors have been added into clinical practice: everolimus and sirolimus. They both have very interesting features, from the point of view of immunomodulation—acting on different stages of the immune system than other agents developed thus far—and for their promising anticancer effects.[5,6]

The immunosuppressive protocols used today after HTx require an early stage of induction, followed by chronic maintenance therapy. Use of a multidrug regimen, acting on different stages of the immune system, can enhance the immunosuppressive effect, reducing the dosages of individual pharmacological agents, and thus reducing their specific side effects. Although this strategy is recognized internationally, the choice of immunosuppressive agent, dosage, and combination of drugs varies from institution to institution. However, the activities of the various immunosuppressive drugs, which affect different phases of the immune response, are still highly nonspecific. The result is an overall decrease of immune responses, including those directed against infectious agents and tumor antigens.[7] For this reason, some of the major long-term complications in patients after HTx are represented by the high incidence of infections and malignancies.

Another mechanism involved in the genesis of post-transplant malignancies is the ability of some immunosuppressive agents, such as azathioprine and some antilymphocyte antibodies such as OKT3, to have a direct oncogenic effect.[8-10] Cyclosporin A may directly contribute to tumor formation through a proneoplastic effect mediated by a selective effect on gene expression in normal cells.[11,12] Therefore, chronic immunosuppressive therapy on the one hand has improved graft preservation and the actuarial recipient survival, but on the other hand, has caused an increased incidence of malignancies. Development of alternative strategies is a necessary topic of research for the scientific community.

Table 1
Mechanisms Contributing to the Increased Risk of Malignancy in Transplanted Patients

- Genetic factors
- Male sex
- High immunosuppression regimen
- Viral infections (HBV, HCV, CMV, EBV, HSV)
- Pre-existing malignancies
- Exposure to sunlight
- Smoking
- Proneoplastic effect of cyclosporin A
- Age > 50 years at transplantation
- Longer survival rate and length of follow-up

CMV, cytomegalovirus; EBV, Epstein-Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HSV, herpes simplex virus.

Although new generations of immunosuppressive molecules directed against new immunologic targets are undergoing preclinical and clinical testing, the real goal of researchers should be the induction of complete immune tolerance in the recipient.[13-18] However, we should consider that it is more difficult to induce tolerance to the heart, as compared with the liver or the kidney.[19] Induced tolerance has been attempted in laboratory studies on HTx in large animals through cell chimerism, peripheral anergy, or combined multiple organ transplantation.[19-21]

Tumors After HTx

In the early days of transplantation, tumors were considered a marginal problem, affecting morbidity and mortality in only a small portion of the population of transplant recipients. With the gradual reduction in acute rejections, graft failure, and infections, through more careful use of immunosuppressive therapy, and the development of antibiotic drugs that are as powerful as they are specific, there has been an increase in the incidence of post-transplant malignancies. This is linked to at least two major interrelated factors: 1) the lengthening of follow-up of recipients, enabled by the increase in their survival; and 2) the increase in the average age of the transplanted population, which has increased by 10 years in the past decade.[22]

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The first observations on the existence of a close relationship between transplantation and cancer originated in the work carried out by Israel Penn, since 1969. At the same time he started what would become the largest and most comprehensive audit log on the incidence of malignancies in transplant recipients, renamed after his death as the Israel Penn International Transplant Tumor Registry (IPITTR). Thanks to the efforts of Penn, who spent over 30 years collecting more than 15,200 cancer cases from all over the world, we now know the characteristics, incidence, and risk factors for cancers arising in patients after organ transplantation. From the IPITTR data, we know that the overall incidence of malignancies in transplant patients is between 4% and 18%, with an average risk of approximately 6% (which is about 10 times greater than that of the nontransplanted population), and a specific risk of developing certain types of cancers increased over 100-fold.[23]

According to some authors, the cumulative risk of developing cancer is even higher, correlating with the duration of immunosuppressive treatment, reaching 20% at 10 years after transplantation, and almost 30% at 20 years.[24,25] There is also unanimous agreement that, in patients who had cancer before transplantation, immunosuppressive therapy may impair the ability of the immune system to control any remaining cancer cells. In fact, data show there is a substantial recurrence of primary disease after transplantation.[26] This is why, in clinical practice, patients who have a history of cancer—unless very remote and clinically cured—are usually excluded from a transplant list. Similarly, organs from donors with neoplastic disease may transmit active cancer cells to the recipient. For this reason, there is a general consensus to exclude patients with current or recent history of cancer from the donor pool. However, recent reports have suggested that appropriately selected patients with a cured pretransplant malignancy can be candidates for HTx.[27]

The IPITTR has documented allograft recipients as developing types of cancer not frequently seen in the general population, with a higher incidence of lymphoproliferative and skin cancers.[28] Within the population of transplanted patients, major differences in the distribution of cancers are detected when comparing patients undergoing cardiac or lung transplantation and patients undergoing kidney transplantation.[29-33] It is clear that the difference in the incidence of cancer would reflect the intensity of applied immunosuppression. Consequently, the neoplastic complications appear to be greater in the first group than in the second. Although Penn considered post-transplantation malignancy as the "price of immunotherapy," the genesis appears to be multifactorial: closely linked to genetic factors, viral, and environmental factors, such as exposure to ultraviolet radiation and smoking.

In consideration of the increased cancer risk in the transplanted population, physicians who treat these patients should have the ability of early detection of the incoming disease. No less important is to teach patients how to prevent and identify the early onset of cancer, to offer them the best therapeutic chance.

Types of Cancer

Important differences in the occurrence rates of neoplasms depend on the organs transplanted. In general, heart transplant recipients have a higher incidence of post-transplant malignancies when compared with

Table 2
Incidence and Types of Malignancies Arising After Heart Transplantation

• Twofold greater incidence of tumors compared with kidney Tx
• Sixfold greater incidence of visceral neoplasms compared with kidney Tx
• Incidence of lymphoma: 42% in heart Tx vs 11% in kidney Tx
• Incidence of lymphoma: up to 82% in pediatric age after heart Tx
• **Skin cancers:** ~ 40% to 50% of total cancers Squamous cell carcinomas have a frequency 40 to 250 times higher than the normal population Squamous cell carcinoma is highest in heart Tx compared with kidney, lung, and liver recipients Multiple lesions (43%) Very aggressive skin cancers
• **PTLD**: incidence of ~ 20% ~ 85% of PTLDs have B-cell origin Multiple organ involvement 70% of cases have visceral involvement
• **Kaposi's sarcoma**: 4% of all post-transplantation cancers (400- to 500-fold increased risk to develop the disease compared with nonimmunosuppressed patients)
• In 399 consecutive patients, cumulative incidence of malignancy by 10 years was 27% (skin malignancy 13%, PTLD 10%)

Data from Tenderich G et al,[34] Lanza RP et al,[35] Penn I,[36] Hamour IM et al,[37] Jensen AO et al,[39] Penn I,[40] Végso G et al,[41] Cockfield SM,[42] and Ferri C et al.[43]

PTLD, post-transplant lymphoproliferative disease; TX, transplantation.

other transplant recipients (Table 2). This difference may be due to the strong immunosuppressive treatment (triple or quadruple therapy regimens) usually used after heart transplantation to prevent rejection. Many renal transplant recipients, however, receive azathioprine/prednisone immunosuppression, and discontinuation of immunotherapy and return to dialysis is possible for them.[34] A higher incidence has been reported for lymphoma and visceral neoplasms when heart transplant recipients are compared with renal transplant recipients.[35,36]

Different incidence of neoplastic disease is reported in the literature. This may be explained by the fact that different immunosuppressive agents may be used by different institutions and changes in immunosuppressant regimens usually affect the resurgence of cancer only in the long term. Introducing or eliminating an immunosuppressant agent from the pharmacological protocol at institutions performing transplantation affects incidence of cancer only in the long term. For this reason, definitive statements on this topic are difficult to confirm at the present time. Despite improvements in pharmacological protocols, Hamour and colleagues[37] still report a cumulative 27% incidence of malignancy by 10 years in 399 consecutive patients after heart transplantation.

Cardiac Allograft Recipients

Cardiac allograft recipients are primarily affected by four major categories of cancer.

Skin cancers. Skin cancers are the most commonly encountered cancer after transplantation, representing approximately 40% to 50% of total post-transplantation cancers. They show a specific risk increased 4- to 21-fold in comparison with the nontransplanted population. Their high frequency is explained by the interaction of various factors, including—in addition to immunosuppression therapy—the exposure to ultraviolet radiation and infection by viruses such as pro-oncogenic human papilloma virus. Their incidence is higher in regions with higher annual exposure to solar radiation; they develop mainly in sun-exposed body surfaces, such as the head, neck, and upper limbs, and in patients with light skin type, blue eyes, and blond or red hair.[38]

In addition, the incidence of skin cancer increases with the level of immunosuppression and with longer follow-up after transplantation. It occurs earlier in older patients. The skin cancer in older patients also assumes different characteristics than in the nontransplanted population. Compared with the nontransplanted population, according to the IPITTR, squamous cell carcinomas have a frequency 40 to 250 times higher; basal cell carcinomas 10 times higher; and melanomas 5 times higher, with an incidence ratio of basal cell and squamous cell carcinomas of 1.8:1 (compared with the ratio of 1:5 in the nontransplanted population). Penn also showed that, in transplant recipients, the frequency of multiple lesions is high (43%), and that neoplasms are very aggressive, with more lymph node metastases and deaths. A recent study reported that squamous cell

carcinoma was highest among heart recipients, followed by kidney, lung, and liver recipients.[39]

Lymphoproliferative disease. The post-transplant lymphoproliferative diseases (PTLDs) represent a spectrum of diseases ranging from lymphatic hyperplasia to lymphoma.[40,41] With the exception of Hodgkin lymphoma and myeloma, which have a lower incidence in transplant recipients, the PTLDs are the second most common malignancy in the transplanted population, with an incidence of about 20%, and with a risk to contract the disease increased 25 to 100 times compared with the nontransplanted population.

From IPITTR immunologic data, it appears that approximately 85% of PTLDs have B-cell origin, 14% have T-cell origin, and 1% have a mixed or undetermined origin. The registry data show that 53% involve multiple organs, whereas 47% are confined to a single organ or site.

Moreover, although in the general population lymphomas most frequently involve lymph nodes, in 70% of transplant recipients they have an extranodal location, affecting the liver (25%), lungs (21%), central nervous system (21%), intestines (19%), kidneys (18%), and spleen (12%). The onset of clinical disease is thus very heterogeneous, able to present with systemic symptoms similar to mononucleosis with diffuse adenopathy, or be more ambiguous and silent, depending on the location.

Several predisposing factors increase the risk of developing PTLD.[42] Approximately 90% to 95% of patients with this type of tumor test positive for the Epstein-Barr virus (EBV). In a healthy subject, there is a positive balance of EBV viral load and immune mechanisms that maintain a persistent infection at a subclinical level. In contrast, in organ transplant recipients, the immunosuppression required to prevent acute rejection is at the expense of T lymphocyte cytotoxic capability, leading to persistent infection, viral replication, and body accumulation of B cells infected with the virus. However, uncontrolled cell proliferation and PTLD development only occur in a minority of EBV patients. There is also evidence in the literature that infections with cytomegalovirus or herpes viruses are risk factors for developing PTLD.[43]

Kaposi's sarcoma. Kaposi's sarcoma (KS) is a rare disease in the general population and shows a higher incidence in organ transplant recipients. It represents approximately 4% of all post-transplantation cancers; the specific risk to develop the disease is increased 400- to 500-fold compared with nonimmunosuppressed patients.[44] There are three possible manifestations of KS: 1) cutaneous form, the most frequent (60%), associated with a more benign prognosis; 2) visceral form, frequently involving the gastrointestinal tract, but also lungs, lymph nodes, heart, liver; it is more aggressive; and 3) mixed form, with characteristics and prognosis similar to the pure visceral form. The diagnosis is easier in the presence of typical skin lesions; it is more difficult when the engagement is visceral, or involves the mouth or throat, necessitating diagnostic imaging and biopsy to confirm the clinical suspicion.

Regardless of the immunosuppressive status of these patients, there seem to be viral cofactors in the genesis of KS. Herpes simplex virus 8 has been identified in many patients with KS, indicating a possible role in its genesis.

Solid tumors. According to IPITTR data, solid tumors affecting the lung, prostate, breast, colon, and cervix are not generally increased in frequency compared with the nontransplanted population.[45,46] In this case, it is difficult even to correlate a single immunosuppressant agent with the genesis of the disease.

Prevention, Monitoring, and Treatment

The follow-up of the heart-transplanted patient includes different screening tests and recommendations for the prevention, surveillance, and management of precancerous and cancerous lesions (Table 3). In the transplanted population, it is the state of immunosuppression on its own that increases the incidence of neoplastic disease, making patients more susceptible to a variety of carcinogens and oncogenic viruses. The prevention of post-transplant malignancies requires a delicate immunosuppression balance between the risk of rejection and the risk of developing cancer. The first objective is to reduce the degree of immunosuppression to the lowest level compatible with a functioning graft. New immunosuppressive agents may reduce the occurrence of malignancies.[47,48]

The follow-up of the heart-transplanted patient includes different screening tests and recommendations for the prevention, surveillance, and management of precancerous and cancerous lesions.

Proliferation signal inhibitors (everolimus or sirolimus) have shown antineoplastic effects together with renal protection and delay of onset of allograft vasculopathy. Therapy with everolimus or sirolimus is indicated in heart-transplanted patients presenting with tumors or in the prevention of their occurrence.[49]

Whenever possible, viral infection should be prevented. For patients on

Table 3
Prevention, Screening, and Management for Post-Transplant Cancer

• Reducing the degree of immunosuppression to the lowest possible dosage
• Vaccination against hepatitis B virus (EBV) in patients on the waiting list
• Antiviral drugs against EBV
• Restriction of sunlight exposure and protection of exposed areas
• Multimodality imaging studies in high-risk patients
• Annual dermatological examination
• Monthly self-skin examination
• Gynecologic examination: annual cytologic cervical cancer screening and pelvic examination once sexually active
• Prostate screening: annual DRE, PSA measurement in men age > 50 years, endorectal ultrasound
• Breast screening: annual or biennial mammography
• Annual chest radiograph and abdominal ultrasound
• Colorectal screening: annual FOBT and/or flexible sigmoidoscopy every 5 years for individuals age > 50 years
• Early treatment of precancerous lesions
• Early treatment by surgery, radiation, and chemotherapy (cautious)
• Therapy with proliferation signal inhibitors (eg, sirolimus or everolimus) may reduce overall cancer risk through an antioncogenic and antiproliferative role
• Therapy with MMF/MPA may reduce risk of PTLD through an antioncogenic and antiproliferative role

DRE, digital rectal examination; EBV, Epstein-Barr virus; FOBT, fecal occult blood testing; MMF, mycophenolate mofetil; MPA, mycophenolic acid; PSA, prostate-specific antigen; PTLD, post-transplant lymphoproliferative diseases.

the transplant waiting list, we vaccinate against hepatitis B, which is closely correlated with the development of hepatocarcinoma. Many institutions also use ganciclovir or acyclovir administered as anti-EBV therapy. There are studies demonstrating its effectiveness in reducing PTLD incidence, even if theoretically, these drugs have only a virustatic effect and do not act on latent viral forms.[50] This therapy seems particularly useful in antiviral prophylaxis in EBV-negative recipients receiving an EBV-positive graft.

Exposure to sunlight, which is closely related to the development of skin cancer, must be severely restricted, especially in those with a light skin type. If the patient's job requires daily exposure to sunlight for several hours (eg, farming or fishing), careful protection of exposed areas with clothing and hats is required.[51,52]

A key role in tumor screening and monitoring is represented by various imaging methodologies, which should be repeated frequently, particularly in patients with higher risk factors. Follow-up of cardiac allograft recipients should include annual dermatological and gynecological examinations, chest radiograph, and abdominal ultrasound. Higher-risk patients require more aggressive surveillance, including colonoscopy, colposcopy, cystoscopy, and endorectal ultrasound.

After diagnosis of a malignant disease, treatment should occur as early as possible, and should also include treatment of precancerous lesions. Nevertheless, initial treatment should also include a reduction in immunosuppression levels. Many cancers, especially skin lesions or localized tumors, may respond to traditional surgical excision, radiotherapy, and chemotherapy. The latter should be introduced with caution because it may add a myelosuppressive effect to the already immunosuppressed patient. Immunosuppression therapy should therefore be reduced before starting any chemotherapy treatment, with the aim to avoid the risk of systemic infections.

Conclusions

Incidence of neoplastic disease is increased in heart transplant recipients. Follow-up after HTx should include frequent and specific tumor screening for early diagnosis and treatment. ■

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Main Points

- Malignant disorders among heart-transplanted patients represent a serious complication, with different mechanisms contributing to the increased risk of malignancies.
- The increased cancer risk in the heart-transplanted population reflects the intensity of applied immunosuppression (higher in comparison with kidney-transplanted patients). However, other factors play a role in the genesis of post-transplant tumors, such as genetic factors and viral and environmental factors (eg, exposure to ultraviolet radiation, smoking).
- Skin cancers are most commonly encountered after transplantation, representing 40% to 50% of all post-transplant cancers. Post-transplant lymphoproliferative diseases (PTLDs) are also common, with an incidence of approximately 20%. Kaposi's sarcoma and solid organ tumors represent other common post-transplant neoplasms.
- Prevention of risk factors, screening for diagnosis, and early management of post-transplant cancer would influence long-term outcome. Reducing the degree of immunosuppression, antiviral vaccination or prophylaxis, reduced sunlight exposure, dermatological examination, and multimodality imaging studies, together with new antioncogenic immunosuppressor therapy may prove valuable in the follow-up of these patients.

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