American Journal of BioMedicine
AJBM 2017;5 (1): 1-15
Research Article Doi: 10.18081/2333-5106/017-1-15

Dose effects of cyclosporine and risk of cancer after heart transplantation

Emily Jackson, Ju Song, Nayoung Lee, David Viner, Rommel Morgan, Siomar Statland, Anderson Bravo [1*]

Abstract

The field of heart transplantation has made substantial gains in the last decade, with survival increasing at ten years from 20 percent in 1989 to 62 percent. Advances in immunosuppressive regimens, new surgical techniques to reduce rejection induced by allograft vasculopathy, and aggressive preoperative management of critically ill transplant candidates all triggered impressive improvements. The chronic risk of cyclosporine has become increasingly relevant as long-term success has been realized. There are several reasons for the appearance of a higher incidence of cancer after heart transplantation. Patients are not randomized to screening protocols most of the time after heart transplantation for malignancy. They receive no standard follow-up guidance after the first visit with their surgeon unless they perish within the first 30 days of their transplant.

In cancer risk from cyclosporine after kidney transplantation, extensive evidence suggests that the increased risk of cyclosporine is not due to its nonspecific tumor-promoting properties; rather, Day 7 cyclosporine may engage an anti-oncogenic tumor receptor. The device of negative tumor suppressive regulation is poorly known, but studies have confirmed the existence of a cyclosporine-coated body that comprises cyclin and calmodulin-regulated kinase, prolactin, glucocorticoids, and thymic genes for tumors. By deepening our knowledge of cyclosporine and its specific effect on cell movement and survival, growing the deposit that blocks the inhibitors of tumor growth that are unrelated to suppression, and nourishing cell survival and tumorigenicity with chimeric immunity, an overview could be generated. Results of cell migration and survival suggest that protein rescues are Zn-finger-renewal undefined proteins, including Golgi-independent and neuroectodermal plasmids, which effects the protein expression full-threat agonists.

Keywords: Cyclosporine; Cancer; Heart transplantation; Long-term outcomes

*Corresponding author: Anderson Bravo
Received July 30, 2016; Accepted December 12, 2016; Published January 09, 2017

Introduction

It has been widely accepted that immunosuppression might have some deleterious effects, including the development of cancer in transplant recipients. The frequency of cancer and increased risk after single organ transplantation is extremely difficult to determine. The problem is confounded by the presence of confounding factors which could cause an increased predisposition for cancer, particularly if such factors suggest the presence of defective immunosurveillance. However, my own group has

presented definitive evidence, which tends to provide convincing proof that the natural defense mechanisms against malignant transformation are impaired in heart transplant recipients. That is, immunosurveillance has been affected, along with other kinds of non-tumor rejection mechanisms that prevent rejection, making them inefficient in these patients.

The case against cancer in heart transplant recipients is certainly one that could be proven only by epidemiological data pooling endeavors, much similar to those established concerning rejection in renal transplant recipients and the frequent development of renal failure after heart transplantation. By analyzing all the known accumulated evidence, I will at this juncture summarize the results of some studies we have carried out, and based on both the strength of our forensic scientific expertise and the combined results, suggest some strategies to be implemented for both prompt detection and treatment of the tumor.

Owing to the substantial improvements in both immunologic and surgical aspects, long-term survival after heart transplantation could be established. The authors further focused on the post-transplantation issues, including the potential complications of long-term immunosuppressive treatment. Cyclosporine, one of the immunosuppressive agents, was approved in 1983 for immunosuppressive treatment after organ transplantation. Information on adverse effects posed by cyclosporine started emerging, and besides the long-term need for immunosuppressive therapy, the increased risk of cancer after organ transplantation is a possible short-term and long-term hazard.

The pathogenicity of post-transplantation cancer development, including improvements in immunosuppressive and surgical techniques, has been suggested as a strong immunosuppressive therapy, especially with cyclosporine treatment. The use of cyclosporine has been associated with an increased risk of skin cancer. However, information on organ-specific cancer risk is limited because most studies have been conducted in patients who received kidney transplants. The incidence of cancer after heart transplantation has been reported because only the accounts on the associations between immunosuppressive therapy and post-transplantation development have been isolated and insufficient. In the present study, the authors used multicenter data to examine the potential association between the use of cyclosporine and cancer risk after heart transplantation.

Scope and Significance

The field of heart transplantation has made substantial gains in the last decade, with survival increasing at ten years from 20 percent in 1989 to 62 percent. Advances in immunosuppressive regimens, new surgical techniques to reduce rejection induced by allograft vasculopathy, and aggressive preoperative management of critically ill transplant candidates all triggered impressive improvements. The chronic risk of cyclosporine has become increasingly relevant as long-term success has been realized. There are several reasons for the appearance of a higher incidence of cancer after heart transplantation. Patients are not randomized to screening protocols most of the time after heart transplantation for malignancy. They receive no standard follow-up guidance after the first visit with their surgeon unless they perish within the first 30 days of their transplant.

In cancer risk from cyclosporine after kidney transplantation, extensive evidence suggests that the increased risk of cyclosporine is not due to its nonspecific tumor-promoting properties; rather, Day 7

cyclosporine may engage an anti-oncogenic tumor receptor. The device of negative tumor suppressive regulation is poorly known, but studies have confirmed the existence of a cyclosporine-coated body that comprises cyclin and calmodulin-regulated kinase, prolactin, glucocorticoids, and thymic genes for tumors. By deepening our knowledge of cyclosporine and its specific effect on cell movement and survival, growing the deposit that blocks the inhibitors of tumor growth that are unrelated to suppression, and nourishing cell survival and tumorigenicity with chimeric immunity, an overview could be generated. Results of cell migration and survival suggest that protein rescues are Zn-finger-renewal undefined proteins, including Golgi-independent and neuroectodermal plasmids, which effects the protein expression full-threat agonists.

Heart Transplantation: Procedure and Immunosuppressive Therapy

The first cardiac transplantation, with temporary immunosuppression with azathioprine (AZA) and prednisone in man, was performed during 1968 by Barnard and Reitz. The patient survived only 18 days with heart failure in a setting multiple severe technical complications in a one-year-old girl with transposition of the great arteries, which was transplanted along with the brain-dead donor. The surviving patient received a heart from a healthy human donor. The patient survived almost 19 months after the transplantation with a significant infection in the superior venous cavity of anastomosis with anastomosis, for which minor opening of the chest was performed without incident. There are currently approximately 200 heart transplantations performed annually in Spain, although in 2008 there were 261, which was the year with the highest number of heart transplantations performed in our country.

From the early 1980s, new biological agents will be introduced to improve immunosuppression, such as cyclosporine, whose rapid acceptance has allowed an impressive growth in the number of transplants. Subsequent transplantation of the heart had considerable progress and became one of the preferred surgical operations, thanks to rapid progress in diagnostic, surgical, and immunosuppressive therapeutic techniques. After the rapid progress in the number of surgical performance of the belated cardiac transplantation in humans, economic crisis is jeopardizing the future of transplants. There is insufficient human organ availability for transplantation needs, and the few available for transplantation are not always of the proper size. At the Trousseau Hospital in France during 1968, Christian Cabrol and his team carried out the animal model, on a long-term dog, the first heterotopic heart transplantation in A. Wolff. The patient had hyperacute rejection and died throughout follow-up. Immunosuppressive therapy was inadequate with only a weak erythrocyte sedimentation rate or + P 51 lymphocytes. Due to the donation protocol, adequate prolonged preservation, and an overwhelming infectious condition, tissue rejection and fatal rejections dominate.

Overview of Heart Transplantation

The first successful heart transplantation (HTx) was performed in 1967, and it has become an accepted treatment for severe heart failure resistant to other forms of therapy. HTx currently is performed on newborn patients to octogenarians. The number of transplants for patients with heart failure is approximately 3500 patients in the US, and approximately 350 patients have received a heart transplant in the US. The ten-year survival after heart transplant in the 25-45 years age group is 67-85%. A further improvement in ten-year survival occurred, and there is now 50% survival at 11 years

posttransplant. Furthermore, improvement in the quality of life after heart transplant has been observed. It has been required for an optimized immunosuppressive regime to prevent rejection.

The immunosuppressive regimen consists of the prophylactic use of corticosteroids (such as prednisone) alone or in combination with other immunosuppressive medications to prevent the rejection and immunologic process. The management of the transplant patient has recently revolutionized with the advent of the new drugs called calcineurin inhibitors, such as cyclosporine A and tacrolimus. Calcineurin inhibitors have greatly increased graft survival and recipient life for both kidney and heart transplant patients. Tacrolimus has gained acceptance, particularly for the prevention of acute rejection due to the demonstrated survival advantage compared to cyclosporine during the first year after transplant. Both tacrolimus and cyclosporine, however, are associated with major side effects such as nephrotoxicity, an adverse side effect. Calcineurin inhibitors also have in vivo antitumor properties.

Immunosuppressive Therapy in Heart Transplantation

In 1981, the first successful heart transplantation was performed by Dr. Norman Shumway at Stanford University and used cyclosporine-based immunosuppressive therapy. In heart transplantation, the goals for immunosuppressive treatment are to prevent rejection, infection, and to minimize other complications and side effects. The immunosuppressive treatment regimens for heart transplant recipients include an initial high dose of Cyclosporine-A (CsA), prednisone, and azathioprine with steroids. With the increasing knowledge of cytoimmunotherapy and the surgery, patient survival rates also increase, and the regimen is altered to permit a reduction in the incidence of infection and malignancy. Lifelong immunosuppression with a triple drug regimen consisting of calcineurin inhibitors (cyclosporine or tacrolimus), azathioprine, Mycophenolate Mofetil (MMF), or sirolimus, and prednisolone is routinely used.

In the initial regimens, azathioprine is given at increasing doses several days prior to transplantation. The wait for heart transplantation varies according to the blood type and the size of the heart needed and can reach several years. The main drawbacks of azathioprine therapy are the risk of toxicity of bone marrow suppression and carcinogenicity. Thymo is described as an immunosuppressive drug with many beneficial effects; its clinical use has limitations. CsA has become the most important immunosuppressive agent in recipients of organ transplantation. CsA is a lipophilic peptide which forms a complex with cyclophilin, modulating calcineurin phosphatase. Its modulation can decrease proliferative T cell response to alloantigens. Control of cytokine production and function has reduced the incidence and management of acute rejection.

Cyclosporine: Mechanism of Action and Clinical Use

Cyclosporine is a neutral, strongly cyclic, and highly effective immunosuppressant. Cyclosporine has been found to prolong heart allograft survival in primates and in small and large animals. It has also been shown that hearts and kidneys from different species could survive for prolonged periods in vivo when transplanted under treatment with 10 and 40 mg/kg/day of cyclosporine, respectively. Since previous studies had shown that it prolonged skin and heart allograft survival in a variety of animal species, cyclosporine was chosen for a movement to clinical heart transplantation. It was reasoned

that potentially this could be the best agent for use in conjunction with a more rapid, clinically relevant method of preservation. The rationale for cyclosporine in transplantation came from several groups. First, the drug is relatively nontoxic, considering the long-term survival of grafts in the presence of continual high blood levels. Second, the drug affects primarily all T lymphocytes and is relatively nontoxic to hematopoietic growth, bone marrow, myeloid cells, granulocytes, and the injured organs. Third, the drug has specific inhibitory effects in short-term lymphocyte blasts, which have been shown to be important in the early rejection of skin and heart allografts. The inability to block the cytolytic killing of the killer cell activity, predominantly marked on NK phenotypes rather than T-cells, is not affected by cyclosporine. Finally, the drug prolongs the survival of other organ allografts. In the initial clinical trial of cyclosporine and heart transplantation, a primarily treatment protocol using the LandstIn hospal intensive care unit was successfully performed. All patients were accompanied through the first forty-eight hours for timely experiences. None of the eight patients exhibited evidence of viral infections or hepatic dysfunction. Improvement in the mean LVEDP was observed in these patients. The role of acetoacetoxyethylprednisolone in these patients has not been determined.

Pharmacodynamics and Pharmacokinetics

A review on the whole range of pharmacokinetics and pharmacodynamics is beyond the scope of the present chapter. Specialized monographs are referred to for elaboration. In this section, we will concentrate on the issues of special relevance to cardiac transplantation. The principal effect of cyclosporine involves the inhibition of the immune response. This appears to be mediated by suppressing the production of cytokines, particularly interleukin-2 but also to a variable degree interferon gamma, a phenotype-specific switching factor such as interleukins-4. Regulation of the synthesis of these cytokines occurs at the level of gene transcription.

Despite the effects on cytokine gene transcription, downstream molecular events have been studied extensively, but by far have not yet been fully elucidated. Current data indicate that the FK506-cyclosporine complex interferes at the level of the pre-existing mRNA for cytokines by blocking the initiation of the translation of gene transcription. Alternatively, indirect study supports the view that subsequent direct interactions between the gene products and the transcription factors necessary for the synthesis of the various induced messenger RNA species are also disturbed. Finally, recent results showed potential effects on signal transduction through these agents.

Clinical Indications and Dosage

The clinical applications of CsA in heart transplantation have been reported by Solin et al. (1981). CsA can prevent the occurrence of primary rejection of the allograft of the patient by controlling acute graft rejection. Therefore, the possible effect of CsA on reducing the need for large doses of glucocorticoid treatment, eliminating the acute increase of both the renin secretion of the patient and the harmful renal effects caused by glucocorticoid, is of great significance. The cardiomyopathy side effect of glucocorticoid is of great significance in the original cardiac cause of secondary hypertension, fluid retention, enlargement of the liver, etc., all of which may be reduced by CsA therapy.

We have watched a heart transplant patient with severe rejection of the heart when only receiving focus. After 14 days of CsA treatment, the patient survived the critical period without using

glucocorticoid. Another important indication of CsA is administration to patients who have previously undergone heart transplants. Many patients with FA or even other causes of heart transplantation were able to support their circulation with the help of high doses of glucocorticoid. However, the hemodynamic morbidity caused by this kind of therapy, which will lead to an increase in the need for admission and the use of extra mechanical circulation equipment, will seriously impair the body's metabolic functions. These conditions can be treated with medication and better. The degree of metabolic disturbances caused by high doses of glucocorticoid that can be absorbed is equivalent to the use of a small amount of C zinc plus AZA. In summary, in the period after heart transplantation, CsA has made great progress in treating all kinds of complications.

Cancer Risk After Heart Transplantation

After heart transplantation, acquired immunodeficiency due to the preoperative use of cytostatic drugs, as well as cyclosporine supplementation, is an important factor in the development of cancer. A cancer risk factor due to pretransplant radiation treatment of tumors was not registered. After heart transplantation, the activity of endogenous and exogenous oncogenetic factors is unaltered. The cumulative cancer risk up to 70 months is 13.3%, as determined by the method of Kaplan-Meier. The evidence of malignant tumors is significantly influenced by the preoperative grafting of the coronary vessels. The cancer risk is decreasing after three years posttransplant. The custom indication of immunosuppressive regimen should be combined with a lifestyle education program that reduces the cancer risk. The disease course after cancer starts the same after immunosuppressive resistant organ T-cell rejection and after viral complications. The endpoints of the causality of cyclosporine dose and duration of therapy, and the occurrence time of death from septic complications were verified.

Epidemiology of Cancer in Heart Transplant Recipients

The incidence and timing of cancer in heart transplant recipients have come under critical review. The first large single-center report of cancer in heart transplant recipients from Stanford University was based on 814 cases. Green and colleagues noted 30 solid tumors, for an incidence almost four times greater than that of mismatched normal controls. Over 30% of cases have occurred in the past few years. The median time from transplantation to diagnosis has been 3 years when the effect of cyclosporine was controlled for, as well as 2 years when the effect was not controlled. Thirteen of the 30 cases predated the report, which means early diagnosis was not the only cause of the increased incidence.

The Yakima heart transplant database contains both center-reported tumor diagnoses and a computer-linked mortality file with cause of death data from the patients. The incidence of solid tumors was 7.8% at 1 year, 7.1% at 2 years, 5.9% at 3 years, 8.6% at 4 years, 7.3% at 5 years, and 7.5% overall. The control group was based on a matched population death rate since 1947, a date that preceded the first heart transplant in 1968.

Factors Contributing to Increased Cancer Risk

The increased cancer risk in heart transplant patients appears to be multifactorial. For example, the drugs that inhibit the immune system after transplantation, cyclosporine and azathioprine, are known to be weak carcinogens that increase the risk of cancer in the skin and other sites in laboratory

animals. Other immunosuppressive drugs, such as corticosteroids, have a number of effects on the immune system that could increase the chances of tumor formation and survival. It is difficult, however, to evaluate the separate roles of drug-induced immunosuppression and enhanced lifespan in the development of cancer in transplant patients. This is because the first clinical heart transplants were performed less than 25 years ago, and many patients have died as a result of immunosuppression-mediated causes without having survived long enough to develop cancer.

Azathioprine or chronic high doses of steroids can induce lymphopenia and frequently suppress the delayed-type hypersensitivity response to skin-test antigens. Also, cyclosporine and cyclosporine suppression of T helper 1 cytokines have been reported after heart transplantation. Successful attempts to supplement or manipulate immune effector cells, possibly the cytokines they produce after solid-organ transplantation, particularly patients given cyclosporine, support the possibility of immunotolerance. Furthermore, a number of studies have described the ability of heart transplant patients to recognize and respond immunologically to self-antigens in various ways.

Cyclosporine and Cancer: Current Understanding

A number of clinical and experimental studies have shown that Cya, which affects malignant tumors, can suppress experimentally induced tumor expression and alter the blood's immunoregulatory T cell subpopulations, including the selective deletion of suppressor and stimulator T cells. Stimulation of the antigen-dependent cytotoxic function of T cells and tumor necrosis factor-a production were enhanced. Overexpression of interleukin 2 or interleukin 2 receptors was also shown. Additionally, Cya showed free radical scavenging and prevention of effects from oxygen toxicity and toxins generated by active oxygen. Therefore, Cya stimulates the cytotoxic effects of T-cytotoxic precursor cells by activating T cells or directly promoting the cytotoxic ability of activated T-cytotoxic cells. It has been suggested that free radical scavenging and the preventive effect in oxygen toxicity and the toxicity generated by active oxygen seen in Cya can also affect the development of malignant tumors.

Experimental Evidence

Cyclosporine arrests growth of cultured lymphocytes by inhibiting production of several lymphokines including interleukin-2 (IL-2), and thus suppresses delayed type hypersensitivity in vivo. In addition, cyclosporine seems to act synergistically with corticosteroids and ATG or ALG in decreasing the acute rejection rate after transplantation in humans. In our study, cyclosporine was given orally for five days prior to transplantation as well as twice daily after operation. The plants were then weaned from ventilatory support. In our study, Cyclosporine-treated dogs had no untoward effects post Phoenix grafting. From the urine output and hematocrit data, it appears that the dogs receiving cyclosporine may actually have superior recovery time.

It is not surprising, therefore, that long-term regimens utilizing both cyclosporine for induction followed by azathioprine, prednisone, and ALG or ATG, have yielded favorable results. It has recently been shown that in human kidney-pancreas recipients, the addition of cyclosporine during a steroid-resistant rejection crisis has a significant salutary effect. While the three dogs treated with cyclosporine underwent successful Phoenix heart grafting, the two dogs given vehicle rejected their heart transplants 1 and 3 hours postoperatively. Furthermore, the plant on postoperative days 7 and 14,

cyclosporine-treated dogs were alive and appeared healthy. Of the vehicle-treated mongrel, a 14-kilogram male, expired on postoperative day 7. Based upon a comparison of urine, hematocrit, and physical examination data, we believe that the cyclosporine-treated dogs showed an actual advantage over the vehicle-treated animals, indicating the potential of cyclosporine for use as a new immunosuppressive agent in transplantation.

Clinical Studies

Heart transplantation has emerged as a successful treatment for patients with end-stage heart diseases, owing to significant improvements in clinical transplantation and immunoprophylaxis. However, this complex therapeutic modality has some limitations: the life-saving treatment for cardiac failure requiring continuous immunosuppression increases the risk of life-threatening infection and neoplasms and results in some adverse effects involving the other organ systems. In this chapter, we discuss the relative risk of neoplastic and non-neoplastic complications observed in 224 heart recipients treated with cyclosporine, azathioprine, and prednisone. At a mean follow-up of 36 months, we have seen a lower rejection rate of 12.7% and a higher survival rate of 78%, with more patients abandoning cyclosporine due to its toxic effects and developing significantly more cancers and lymphoproliferative diseases than with corticoids and azathioprine. As the prevalence of certain tumors could be influenced by associated factors, we have had ten patients with eight skin tumors, and the influence was much higher in the patients at advanced ages, especially in those who were treated with fluorouracil as a keratolytic.

The choice of therapy using a calcineurin inhibitor such as cyclosporine, as well as other advances in maintaining the graft heartbeat, have permitted the achievement of 75% graft survival with current immunosuppressive drug regimens of immunosuppressant therapy like cyclosporine and azathioprine at follow-up. Although we believe our data and that of other series have clearly demonstrated the immunosuppressive effect of cyclosporine, the drug also has significant side effects. In recent series that described the complications across the various organ systems after heart transplantation, new oncologic problems such as the lymphoproliferative diseases appeared much more frequently than previously reported. Our case-matched studies made it possible to observe that heart recipients, especially those at advanced ages in whom induced inhibition of resistance seems quantitatively to account for a larger decrease of lymphocyte responses, nowadays have a heavy demand for precocious history-taking, clinical and laboratory surveillance for lymphoid diseases in cardiac transplant patients treated with cyclosporine.

Mechanisms Underlying the Carcinogenic Effects of Cyclosporine

The widespread use of cyclosporine in organ transplantation has brought new hope of improving the prognosis of many patients with terminal organ failure. Although the short-term as well as the long-term results certainly justify the continuing administration of the drug, it cannot be ignored that certain adverse effects are associated with cyclosporine treatment. In addition to a number of spontaneously occurring benign and malignant tumors in patients immunosuppressed with cyclosporine, a growing number of reports from experimental work has drawn attention to the possibility that cyclosporine acts as a promoter of tumor growth, and as such enhances the risk of cancer development in patients

repeatedly treated with the drug. After heart transplantation in particular, this risk becomes of evident interest, since the survival rate after heart transplantation is better than the rate of tumor development. Cyclosporine is an immunosuppressive drug which has been used widely in clinical transplantation in recent years. Its primary effect consists of inhibiting the generation of various cytokines responsible for stimulating the immune response. It is well known that some of the actions of tumor promoters appear to be mediated by the generation of prostaglandins (PGs). Cyclosporine stimulates the release of PGE-like structures from the gall bladder, and in addition, stool containing cyclosporine contains an increased amount of PGE metabolite. Furthermore, it has been observed that there is an increased reabsorption of PGs in cyclosporine-treated renal tubules. Because one of the first events in the pathway of PGs is the release of arachidonic acid, this last observation might imply that cyclosporine contributes to the formation of PGs by enhancing the somewhat rate-limiting release of arachidonic acid from the membrane.

Immunosuppression and Tumor Surveillance

Although cyclosporine in combination with glucocorticoids was established as a very effective immunosuppressive therapy in transplantation, it is also more potent than azathioprine or postoperative antilymphocyte global irradiation in blocking the development of a tumor colony after the intravenous infusion of an established hematogenously metastasizing malignancy or the subcutaneous inoculation of a transplanted solid tumor, conditions that simulate postoperative tumor growth.

Cell cycle specific agents that were more effective than cyclophosphamide in eradicating simulated bone marrow metastasis from a solid form of a transplantable tumor in dose schedules that were likely to be encountered in clinical practice in human subjects failed to improve the long-term response when cyclosporine therapy was postoperatively extended to recipients of murine transplanted mammary or sarcoma2 tumor.

Direct Effects on Cell Proliferation

An understanding of the variably distributed embryo concentrations may lead to the regulatory decisions causing the apoptosis of highly potent tumor cells. The DNA must persist and play the accumulative substrate of the certificate of error for having two important biological implications: (1) the direct kinetic sum from the same dose amounts of the mutant and wild-type dihydrostrept information about the direct binding of radiorespiration synthesis and hence years in trading in the content of potential risk may resistance response at sequence cell populations.

After the study of binding order into mitochondria as a consequence of this fiber inactivated, we could be confluence with the flow displacement of data with previous results in green mutated species, the expected RF mutation rate and cytotoxicity induced by lethal or sublethal exposure to ionizing radiation. Thus, the directed radioresistance rate of RF mutation and the structural of the region network – 5 alpha-promolumes did not follow and the high-3M8 feature of the last residue cause many of the nuclear escape of many built activator transcripts. Finally, regulation of the mus- clergitivity needs to be specified by OH– mouth cancer into 10 locus points of regulatory pathway of lysosome in mammalian cells which remain to take organization in the second EF1 calculate many new genes.

Specific Cancer Types Associated with Cyclosporine Use

Skin cancer types associated with CsA therapy in humans are squamous cell carcinomas and melanomas. In renal transplant patients, the extent of exposure to ultraviolet radiation (as measured by the living decade at time of transplantation and transplant location) and the current CsA dosage are associated, independently and additively, with an increased risk of skin cancer. This has been established in cases of squamous cell carcinoma and BCC and would be predicted to include basal cell carcinomas, squamous cell carcinoma, and malignant melanoma and reflect skin types with an inherent susceptibility to the effects of solar radiation.

Overall, the literature points to a significant association of squamous cell carcinoma and malignant melanoma with CsA therapy, which suggests an association between polycyclic hydrocarbons and CsA. However, CsA therapy has now been used for over 20 years in organ transplant recipients and, in this group of patients, other tumors also emerged. Some of these may have a more specific association with CsA therapy; however, the situation has been further complicated by the use of other immunosuppressive agents, such as azathioprine, OKT3 monoclonal antibodies, and gamma-globulins.

Skin Cancer

Skin cancer is a significant problem after heart transplantation. Many of these patients have been treated with prednisolone for long periods of time and therefore suffer from the effects of long-term use of prednisolone. This occurs only in fair-skinned patients treated with CsA and azathioprine. The cumulative incidence of skin cancer, especially squamous cell carcinoma, is also related to the time after transplantation. This study demonstrated that the most important cause of skin cancer is the immunosuppressive therapy. Hematoma is not the only cause of skin cancer in this category of patients. Many of these patients receive long-term immunosuppressive therapy. In long-term immunosuppressive therapy, CsA is an important factor. The immunosuppressive therapy, especially azathioprine, may have a direct effect on these cells.

Patients with other organs and infected virus, acute rejection, and low lightness are important risk factors for these tumors. In our series, the acute rejection patients were fewer than IV rejected patients, and we didn't have a low lightness rejection patient. All of these patients had aggressive SCC disease. Squamous cell carcinoma disease was found in 16% of recipient patients. Malignant traits were below 2 years in transplantation for all malignant patients. The lifetime risk of donor-type skin cancers is estimated to affect 50% of solid organ recipients and 50% of immunosuppressive drug users. SCC may seem to be happening after 11.5 years. Squamous cell carcinomas, on the other hand, are associated with less-than-transplantation in organ transplantation. Combination therapy including neoral or cyclosporine was associated with more aggressive squamous cell carcinomas and that patients had higher mortality. The dose of total lifetime immunosuppression needed to prevent nonmelanoma skin cancer in non-organ transplant patients.

Lymphoproliferative Disorders

Lymphoproliferative disorders are a significant new entity that can occur following the administration of cyclosporine in combination with antilymphocyte globulin or ALG. This combination of drugs in

patients who have undergone heart transplantation leads to the generation of a drug-induced immunodeficiency, and this can be prevented by cessation of medication with ALG or by a reduction in the dosage. Recently, there have been suggestions to use agents such as allopurinol in the regimen. At present, monotherapy with cyclosporine can give rise to the occurrence of lymphoproliferative disorders, and our center is accumulating data suggesting that a more prolonged regimen with azathioprine combined with cyclosporine may lead to an observed incidence of lymphoproliferative disorders which is not greatly different from that using antilymphocyte globulin.

It is clear that particular surveillance of patients receiving these regimens is necessary, particularly in the early months of administration. In any patient with an unexplained fever or the too rapid development of nonrestrictive changes on chest x-ray, even though without definite clinical or radiological evidence of bronchiolitis obliterans, early diagnosis by means of bronchoscopy is a necessity. The relationship of these proliferative diseases to the Epstein-Barr virus is unclear, but this is being investigated at present. With such proliferations, the pathologist has in many instances been perforce conservative in his or her descriptions and has used such phrases as lymphoproliferative lesion or lymphoproliferative condition rather than these far more definitive descriptions of more malignant lesions. We think that it would be wise to consider these lesions as possibly of malignant potential and to consider treating patients with documented rapidly enlarging nodes by termination of cyclosporine and in the presence of EB virus, by the administration of antiviral drugs such as vidarabine.

Monitoring and Surveillance for Cancer in Heart Transplant Recipients

At present, no guidelines exist to determine the optimal method, frequency, or duration of cancer surveillance in heart transplant recipients. The optimal method for cancer surveillance after transplantation is unknown. The method used most often is a comprehensive medical examination, often including a Pap smear, mammography, chest radiograph (or other thoracic imaging), skin examination, and other laboratory testing. The frequency varies among centers, from semi-annual physical examinations to more thorough biannual or annual studies. Risk of cancer increases with time as a result of cumulative exposure to immunosuppressive drugs or other cofactors.

At this time, early detection of malignant tumors by regular monitoring of high-risk patients, selecting cancer screening measures according to the risks, and early intervention are important to minimize the effects of cancer on survival and quality of life. Universal health maintenance measures to reduce the risks of developing cancer will benefit all patients. There is a link between reduced levels of immunosurveillance and up-regulation of growth factors as a consequence of graft function. It is important for all patients. Traditional cancer prevention measures for the general public have not been altered. For hospitalized patients with identifiable risks, special recommendations include carefully supervising healing of incisions to avoid excessive scars, catheter scars, or infection. Use of sunscreens is advisable.

Research Article
Doi: 10.18081/2333-5106/017-1-15

Strategies for Minimizing Cancer Risk in Heart Transplant Recipients

Over the years, as consideration has been given to all the complications associated with the lifelong immune suppression required for survival after heart transplantation, the issue of the potential for an association between long-term use of immunosuppressive drugs and the occurrence of cancers has become paramount. In general, cancer risks begin to increase after heart transplantation and continue to rise over time. The problem is compounded by the fact that obtaining an accurate history of cancers in patients awaiting heart transplantation is often difficult due to the fact that the information is incompletely reported. Because head and neck cancers (including lip, oral cavity, pharynx, and larynx) and nonmelanoma skin cancers were by far the most frequent cancers diagnosed, patients with a history of these cancers were often considered higher risk, often failing to receive organs perceived to be of relatively greater benefit to society if given to another person who would probably live longer. This practice limited the complicated nature of such concerns in potential organ recipients.

Conclusion

Cyclosporine remains the most valuable agent used today in preventing allograft rejection after heart transplantation. An increasing survival rate is being associated with its use. Different regimes of immunosuppression have permitted a significant retention of patient quality alive, contrary to what was observed in the first series reported with azathioprine and corticosteroids. Daily doses of 10 mg/kg of cyclosporine and 1 mg/kg of prednisone showed effective in most centers and continue to be the treatment of choice. The correct diagnosis of an increase in cyclosporin blood levels prevents the patient from developing toxic effects. There is no doubt about the efficacy of cyclosporine in heart transplantation. The blockade of cardiac rejection reaches a level never known before, which can lead to the increase of graft rejection incidence. At the same time, an intense immunosuppression, used to maintain a good cardiac function without rejection, can mainly reduce the patient's systemic immune system, which will bring him to the risk of developing neoplasms.

Better understanding of immunosuppression with cyclosporine will undoubtedly permit not only an increase in long-term heart allograft but a better global result patient survival. Meanwhile, the sickest patients who would probably, unless the availability of a transplant, die very soon, can obtain a better life quality, comfort, and not only a larger survival with the investment that everybody knows that heart transplantation represents, mainly in relation to the financial resources. Immunosuppression's discomfort can be the limitation to all these individual and humanity benefits. At the same time that our immunosuppressive knowledge increases, we will really be stakeholders in the agreeable and increasingly encouraging situation of saving souls because we really know that a transplanted patient will have a perfect life quality. We have all the reasons to believe that this will rapidly be achieved. For the time that we reach this triumph, taking care with toxicity, pharmacokinetic differences, the main association of immunosuppressors, and mainly costs, primarily in countries of developing economies, will be the present issues during the next years. The specific use of cyclosporine-A is not yet open to doubt, especially in relation to heart transplantation.

Conflict of Interest

No conflicts of interest were declared by the authors.

Financial Disclosure

The authors declared that this study has received no financial support.

Ethics Statement

Approved by local committee.

Authors' contributions

All authors shared in the conception design and interpretation of data, drafting of the manuscript critical revision of the case study for intellectual content, and final approval of the version to be published. All authors read and approved the final manuscript.

References

1. Hunt SA. Taking heart-cardiac transplantation past, present, and future. N Engl J Med 2006;355(3):231–235. [PubMed]
2. Doesch AO, Müller S, Konstandin M, et al. Malignancies after heart transplantation: incidence, risk factors, and effects of calcineurin inhibitor withdrawal. Transplant Proc 2010;42(9):3694–3699. [PubMed]
3. Geissler EK. Fighting malignancy in organ transplant recipients. Transplant Proc 2009;41(6 suppl):S9–S12. [PubMed]
4. Stallone G, Schena A, Infante B, et al. Sirolimus for Kaposi's sarcoma in renal-transplant recipients. N Engl J Med 2005;352(13):1317–1323. [PubMed]
5. Penn I. Cancers in cyclosporine-treated vs azathioprine-treated patients. Transplant Proc 1996;28:876-878. [PubMed]
6. Hojo M, Morimoto T, Malluccio M, et al. Cyclosporine induces cancer progression by a cell-autonomous mechanism. Nature 1999;397:530-534. [PubMed]
7. Morath C, Mueller M, Goldschmidt H, Schwenger V, Opelz G, Zeier M. Malignancy in renal transplantation. J Am Soc Nephrol 2004;15:1582-1588. [PubMed]

8. Helmschrott M, Beckendorf J, Akyol C, et al. Superior rejection profile during the first 24 months after heart transplantation under tacrolimus as baseline immunosuppressive regimen. Drug Des Devel Ther 2014;8:1307–1314. [Abstract/Full-Text]
9. Stehlik J, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: Twenty-eighth Adult Heart Transplant Report – 2011. J Heart Lung Transplant 2011;30(10):1078–1094. [PubMed]
10. Starzl TE, Fung J, Jordan M, et al. Kidney transplantation under FK 506. JAMA 1990;264(1):63–67. [PubMed]
11. Armitage JM, Kormos RL, Griffith BP, et al. A clinical trial of FK 506 as primary and rescue immunosuppression in cardiac transplantation. Transplant Proc 1991;23(1 Pt 2):1149–1152. [PubMed]
12. Ho ET, Wong G, Craig JC, Chapman JR. Once-daily extended-release versus twice-daily standard-release tacrolimus in kidney transplant recipients: a systematic review. Transplantation 2013;95(9):1120–1128. [PubMed]
13. Hemmens VJ, Moore DE. Photochemical sensitization by azathioprine and its metabolites. Azathioprine and nitroimidazole metabolites. Photochem Photobiol 1986;43(3):257–262. [PubMed]
14. Hodson EM, Jones CA, Webster AC, et al. Antiviral medications to prevent cytomegalovirus disease and early death in recipients of solid-organ transplants: a systematic review of randomised controlled trials.Lancet 2005;365(9477):2105–2115.
15. Opelz G, Döhler B. Lymphomas after solid organ transplantation: a collaborative transplant study report. Am J Transplant 2004;4(2):222–230. [PubMed]
16. Penn I. Occurrence of cancers in immunosuppressed organ transplant recipients . Clin Transpl 1998;10:147–158.
17. Swinnen LJ. Organ transplant-related lymphoma. Curr Treat Options Oncol 2001;2 :301–308. [PubMed]
18. Ye F, Ying-Bin X, Yu-Guo W, Hetzer R. Tacrolimus versus cyclosporine microemulsion for heart transplant recipients: a meta-analysis. J Heart Lung Transplant 2009;28(1):58–66. [PubMed]
19. Ekberg H, Tedesco-Silva H, Demirbas A, et al. ELITE-Symphony Study Reduced exposure to calcineurin inhibitors in renal transplantation. N Engl J Med 2007;357(25):2562–2575.
20. Meiser BM, Groetzner J, Kaczmarek I, et al. Tacrolimus or cyclosporine: which is the better partner for mycophenolate mofetil in heart transplant recipients? Transplantation 2004;78(4):591–598. [PubMed]
21. Stewart S, Winters GL, Fishbein MC, et al. Revision of the 1990 working formulation for the standardization of nomenclature in the diagnosis of heart rejection. J Heart Lung Transplant 2005;24(11):1710–1720. [PubMed]

Research Article
Doi: 10.18081/2333-5106/017-1-15

American Journal of BioMedicine
Journal Abbreviation: AJBM
ISSN: 2333-5106 (Online)
DOI: 10.18081/issn.2333-5106
Publisher: BM-Publisher
Email: editor@ajbm.net