Cyclosporin-A associated malignancy

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Abstract: The use of cyclosporin is well established within the ophthalmology community, especially against sight threatening intra-ocular inflammation. It is well known however, that immunosuppression in general is a risk factor for the development of malignancy and numerous studies point to the risk imposed by cyclosporin. This article analyses and reviews all relevant studies with regard to the development of malignancy associated with the use of cyclosporin and extrapolates this into the ophthalmic setting. This is to enable clinicians to assess the risks in individual patients and to present a monitoring regime which can be used in patients undergoing cyclosporin treatment. The review is solely concerned with the risk of the development of malignancy following cyclosporin immunosuppression and not with any other adverse effect.
Keywords: cyclosporin, ciclosporine, cyclosporine, malignancy, neoplasm and cancer development

Background

Uncontrolled ocular inflammation is an important cause of visual loss. The incidence of blindness due to uveitis is, for example, similar to that due to diabetic retinopathy amongst people of working age (Tremblay et al 2002). 70% of patients attending a uveitis clinic have been reported to have vision worse than 6/18 (Durrani et al 2004). In order to prevent or treat these potentially blinding conditions, a variety of drugs are used to suppress the immune response. Traditionally corticosteroids have been used but in more recent years the use of cyclosporin A (CsA) has become more widespread as monotherapy or in combination with other immunosuppressive agents.

The discovery of the immunosuppressive action of CsA in 1976 by Borel et al (1976, 1977) began a new era in immunopharmacology. It was the first immunosuppressive drug that allowed selective immunoregulation of T cells without excessive toxicity. It is now commonly used for immunosuppression following organ transplantation, treatment of graft-versus-host reactions following bone marrow transplantation, in the treatment of rheumatoid disease, psoriasis and severe forms of atopic disease. Its use in ophthalmology is well established.

CsA use is associated with several significant adverse reactions. Most of these, such as its effects on renal function or blood pressure, are well recognized and regimes for monitoring patients on CsA are well established. The risk of the development of malignancy is however, a very important consideration and it is not uncommon following organ transplantation. The risk of the development of malignancy associated with the use of CsA in an ophthalmic setting is not clear. This review aims to collate previous studies regarding the development of malignancy and suggest guidelines that should be adhered to when commencing this treatment in the ophthalmology setting.

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Literature review

A literature search was carried out into cyclosporin and malignancy using the Medline search engine. There is no relevant publication in the Cochrane library. Several searches were performed using combinations of cyclosporin, ciclosporine, cyclosporine,

malignancy, neoplasm and cancer development. The extensive results were filtered for relevancy and all articles that were concerned – either primarily or secondarily – with malignancy development following the use of CsA were reviewed. One non-English language publication was encountered and abstract translation was sufficient for its use. All articles that were considered eligible were analyzed and weighted according to the usual hierarchy of evidence – RCT's, cohort studies, case-control studies, cross-sectional surveys then case reports.

Mechanism of action

Cyclosporin is a lipophilic, cyclic endecapeptide consisting of 11 amino acids and is produced as a metabolite of the fungus species *Tolypocladium inflatum and Cylindrocarpon lucidium*. It was initially discovered by Borel and his co-workers in their studies of screening fungal products for antifungal activity (Borel et al 1976). Nine cyclosporins have been isolated (A to I) but only A, C and G exhibit any immunological activity (Yocum 1993). The immunosuppression caused by CsA is most effective against T cell dependent immune mechanisms, which are implicated in transplant rejection and some forms of autoimmunity. The immunosuppressive activity of CsA is the result of the inhibition of T-helper cells and cytotoxic T-cells, suppressor T-cells being less affected. CsA blocks cytotoxic T cell activation by initially binding to the cyclophilin family of proteins which in turns recruits calcineurin, inhibiting its action. This causes inhibition of the formation of a calcineurin-dependent factor, essential for the transcription of the interleukin-2 gene, thereby reducing production of IL-2 by activated T cells and inhibiting expression of IL-2 receptors by cytotoxic T cells. CsA also selectively blocks many immunoregulatory functions of activated T-cells inhibiting the release of IL-3, IL-4, IL-5, interferon γ, GM-CSF and TNF-α. A further action of CsA is to increase expression of TGF β; a potent inhibitor of IL-2 stimulated T cell proliferation and inducer of fibroblast growth. A further mechanism that amplifies the immunosuppression is the induction of T cell apoptosis which happens with most immunosuppression agents.

Cyclosporin can be given orally, by intravenous injection or topically. Systemic administration achieves peak plasma concentration within 3–4 hours. It has a plasma half-life of around 24 hours and plasma concentration can be determined by radio-immunoassay. CsA accumulates in most tissues at a concentration 3–4 times that measured in the plasma. CsA is extensively metabolized in the liver by cytochrome P450 3A enzyme and also, to a lesser extent, by the gastrointestinal tract and kidneys. The metabolites are mainly excreted via the bile into the faeces; however, 6% is excreted via the kidneys and 0.1% is excreted unchanged in the urine (Rang et al 1990).

Tumor pathogenesis

Longstanding immunosuppression – whether iatrogenic, acquired or due to inherent defects of the humoral or cellular immune response – is associated with increased risk of malignancy. This is especially true of those tumors where oncogenic viruses play a role in the pathogenesis. The commonest tumors associated with immunosuppression are skin cancers with 90% of these being either squamous (SCC) or basal cell carcinomas (BCC) (Euvard et al 2003). SCC has been estimated to occur 65–250 times as frequently as in the general population and BCC 10 times (Hartevelt et al 1990). All SCC's are more aggressive in immunosuppressed patients with more rapid growth, recurrence in 13.4% of patients and metastases in 5 to 8% (Euvard et al 2003). Kaposi sarcoma (KS) is also far commoner in the immunosuppressed population. A viral cause of KS was confirmed in 1994 by the discovery of human herpes virus 8 (HHV-8) and it is the geographic distribution of this virus that may be the cause of the ethnic differences seen (Boshoff and Weiss 2001).

Lymphoproliferative disease is the second most common malignancy in the chronically immunosuppressed but it is seen as a far greater risk due to the associated mortality. Post transplant lymphoproliferative disorder (PTLD) is a spectrum of malignancies that range from mononucleosis to frank lymphoma. There is strong evidence linking EBV with non-Hodgkin's lymphoma (Caillard et al 2005), and emerging studies linking CNS lymphoma with CMV and polyomavirus (Del Valle et al 2004). Immunosuppression is heavily implicated in the pathogenesis of PTLD either due to the reduced immuno-modulation of EBV, absence of T lymphocyte control over benign lymphoproliferation or the over-stimulation of a depressed immune system by chronic antigen stimulation from transplanted tissue.

It has been estimated that over the next 20 years, post-transplant malignancy will become the leading cause of mortality in solid organ transplant recipients with current estimates placing the incidence of malignancy at 20% in the chronically immunosuppressed (Guba et al 2004). The etiology is very complex and multifactorial, for this review we will concentrate on the research implicating CsA. As the review shows, CsA may carry a higher risk of some malignancies than other immunosuppressive agents, various theories have been postulated to account for this.

Synthesis of TGF-β

CsA promotes cancer progression by inducing TGF-β production (Hojo et al 1999). Virtually every cell in the body produces and has receptors for TGF-β. This cytokine regulates both the proliferation/differentiation of cells and stimulates both the production and the adhesiveness of the extracellular matrix by stimulating fibroblasts and other cells to produce extracellular matrix proteins and cell adhesion proteins. It also decreases the production of enzymes that degrade the extracellular matrix, including collagenase, heparinase and stromelysin and increases the production of proteins that inhibit these enzymes, such as plasminogen-activator inhibitor type 1 and tissue inhibitor of matrix metalloprotease. The net effect is an increase the production of extracellular matrix proteins and changes to the adhesive properties of cells. In cancer cells the production of TGF-β is upregulated, increasing the invasiveness of the cells by increasing their proteolytic activity and promoting binding to cell adhesion molecules. The production and secretion of TGF-β by certain cancer cells suppresses the activities of infiltrating immune cells, helping the tumor escape host immunosurveillance. In addition, animal studies (Guba et al 2004; Shihab et al 2003) indicate that subsequent tumor development may be related to an enhancement of tumor angiogenesis possibly due to an increased expression of vascular endothelial growth factor (VEGF). Both increased production of TGF-β and VEGF will work to enhance tumor progression but neither will initiate oncogenesis.

Inhibition of DNA repair

CsA inhibits both Ultraviolet-B induced apoptosis and DNA repair in normal keratinocytes following UVB irradiation (Yarosh et al 2005; Kelly et al 1987; Herman et al 2001). The study by Herman took peripheral blood monocytes from renal transplant patients and induced DNA damage by UV irradiation. They found that CsA treated patients had significantly poorer DNA repair than those patients treated by azathioprine or prednisolone (or in combination). Ahlers et al (1999) proved that CsA inhibited the gene coding for DNA polymerase Beta – a DNA repair enzyme.

Apoptosis alteration

The published evidence of the action of CsA on apoptosis shows that depending on cell type and conditions, CsA can induce or inhibit the process. It is well recognised that CsA (and immunosuppression in general) can cause apoptosis of T cells (Fellstrom and Zezina 2001); however, several studies have shown CsA to have a anti-apoptotic effect (Andre et al 2004) due to its binding with cyclophilin D which in turns inhibits a permeability pore opening in mitochondrial inner membranes which is the trigger for apoptosis initiation.

All these biochemical actions of CsA theoretically work in conjunction with one another to cause and promote cancer development. The initial DNA mutation may be caused by sunlight (skin tumors) or oncogenic viruses (such as EBV, implicated in PTLD and HHV-8 in KS) but CsA causes impaired DNA repair leading to mutated DNA. This cell should undergo apoptosis but this process can be inhibited by CsA and the induction of TGF-β/VEGF works to promote tumor progression.

Neoplasms associated with non-ophthalmic use of CsA

The majority of studies regarding the development of malignancy following CsA use stems from transplantation research. Penn's work (Penn 1987a, 1987b; Penn and Brunson 1988) using the Cincinnati Tumour Registry was the first to raise the possibility of an association between CsA use and the risk of malignancy, especially Non-Hodgkin's Lymphoma (NHL) and Kaposi's sarcoma (KS). Somewhat paradoxically though, the report also states that other skin cancers occurred *less* commonly than in those patients treated by conventional immunosuppression. The conclusion was that the neoplasms were probably not specific to CsA therapy but appeared to be a complication of immunosuppression in general. More recently a retrospective analysis of patients who developed malignancy following renal transplantation noted that, since the introduction of CsA, the incidence of tumor diagnosis had increased compared with the era of conventional immunosuppression, but only in patients over 45 years at the time of renal transplantation. The most frequent cancers reported were skin and genitourinary (Tremblay et al 2002). Figures from the post-marketing surveillance study – which monitors organ transplant patients for 7 years after surgery, a total of 10,454 patient years – showed that following transplantation, CsA increases the overall risk of malignancy two fold (Cockburn and Krupp 1989).

A retrospective study of 633 renal transplant patients, 438 of whom received CsA as part of the immunosuppression regime, reported a significantly higher number of malignancies developing in the four year follow-up period in those patients undergoing CsA use when compared with those undergoing conventional immunosuppression. Skin and genitourinary cancers were the most common malignancies. An interesting point is that after an extended follow-up period for those patients treated with more conventional

immunosuppression, the rate of malignancy development increased (Schmidt et al 1996). An open randomized study took two cohorts of renal transplant patients that were randomized 1-year after transplantation. One group received low dose CsA and the second a normal dose group. They were followed for an average of 66 months. Of the initial 231 patients, 60 developed malignancy, 37 in the normal dose group and 23 in the low dose group ($p < 0.034$), the majority being skin cancers. There was no evidence that halving trough blood CsA concentrations significantly changed graft function or graft survival and that the low dose regimen was associated with fewer malignant disorders (Dantal et al 1998). McGeown et al (2000) showed that patients who received a higher dose of CsA (4.5 mg/kg/day) had a significantly higher rate of tumor development than those on a dose of 3.4 mg/kg/day ($p = 0.014$). A recommendation was made to keep the dose of CsA to less than 3.5 mg/kg/day in long surviving, stable renal graft recipients in order to minimize the risk of developing malignancy. The commonest malignancies seen in the report were SCC, BCC and lymphoproliferative disease.

The multicentre Collaborative Transplant study (Opelz and Henderson 1993) published the rates of NHL development in 52,775 transplant recipients and reported on the associated risk factors. They concluded that there were four factors in the development of NHL; heart rather than kidney transplant, geography, antithymocyte/antilymphocyte globulin or the monoclonal anti-T-cell antibody OKT3 use and use of a combination of CsA and azathioprine (RR 1.47) however they did not find any increase in NHL when CsA was used alone. A retrospective study by Libertiny et al (2001) followed 1501 patients that underwent renal transplant with immunosuppression over a 23 year period, again specifically looking at the rates of lymphoproliferative disease. The majority of their patients had a dose of CsA between 8 and 10 mg per day, aiming for a trough level of 150–300 ng/ml. They concluded that over the years there had been two distinct changes in the rates of lymphoproliferative disease. The first change occurred around the introduction of CsA into clinical practice after which an increase in the rate of PTLD was seen. The second increase in PTLD rate occurred around the early 1990s, completely independent of CsA use and may have reflected a change in the pre-transplant transfusion rates. This study underlines the complexity of the subject and the differing conclusions that exist in the literature.

KS seems to be more severe after CsA immunosuppression rather than conventional immunosuppression. Farge (1993) reported upon the patients on the Groupe Collaboratif de Recherche en Transplantation de I'Ile de France (GCIF) registry. Of the 7923 patients analyzed, 0.52% developed KS in the follow up period. They found that KS was significantly more common following liver transplantation and followed a more severe course in those patients treated by CsA rather than conventional immunosuppression. A report on 50 patients who had developed malignancy following renal transplantation showed that KS was found in a higher proportion of patients that had undergone immunosuppression with CsA than the more conventional treatment (Haberal et al 2002). Montagnino et al (1994) reported on 13 from 820 renal transplant patients who developed KS following transplant. 11 of the 13 were on CsA. In all patients immunosuppression was modified and 9 of these 11 showed disease remission. Two patients died due to intestinal lesions but in these cases immunosuppression had been reintroduced following partial remission of the disease. An early report of KS (Little et al 1983) showed regression of the disease when CsA dose was reduced to below 100 mg/day. Marcen et al (2003) performed a retrospective analysis of 793 patients who had undergone renal transplantation. Although there was no segregation of immunosuppression regimes, 7 of 8 patients who developed KS were treated with CsA. CsA was a significant risk factor for the development of malignancy with an odds ratio of 4.45. A report of two cases of KS in kidney transplant patients who had been treated with azathioprine, steroids and CsA; during this treatment the Langerhans cells decreased and KS appeared. Discontinuation or reduction of the dosage of CsA led to complete regression of the illness. The Langerhans cells reappeared leading to the suggestion that CsA damages the immunological function of the epidermal Langerhans cells and that this was the primary factor in the development of KS (Bedani et al 1999).

Immunosuppression can be used in cases of severe rheumatoid arthritis (RA). Arellano and Krupp (1993) reported the results of a large study of over 1000 patients with RA who were treated with CsA. 17 patients developed a malignancy in the follow up period (which was in excess of 34 months) leading to the conclusion that although RA itself increases the risk of malignancy, the use of CsA leads to an additional risk, especially of lymphoproliferative disorders where the risk increased 3.5 fold. Of the 17 who developed malignancy, only 2 received more than 5.0 mg/kg/day CsA.

CsA is used extensively in the treatment of dermatological disease. Grossman et al (1996) reported on 122 dermatology patients who had been treated with CsA for plaque psoriasis with doses ranging from 2.5 to 5 mg/kg/day for a treatment time of 3 to 76 months (median 21.5 months).

In this study, 5 patients developed a malignancy, two during the treatment period and three following discontinuation of CsA. This study had only a short follow-up time and may not have detected some cases that developed later. Marcil and Stern (2001) investigated 22 patients who were taking CsA for psoriasis, who had previously had PUVA phototherapy. There was a comparison made between the rate of SCCs that developed before CsA administration and the rate afterwards. CsA use significantly increased the incidence of SCC above that from PUVA phototherapy alone. Unfortunately details of the dosages used were not reported. Paul et al (2003) published a prospective, 5-year observational study of 1252 psoriatic patients treated by CsA and their malignancy rates. Malignancies were diagnosed in 3.8% of patients, 49% being skin malignancies and the majority being SCC. There was a six-fold higher incidence of skin malignancies than in the normal population with patients treated for more than 2 years having a higher risk of SCC development. The incidence of other malignancies was not significantly higher than in the general population.

Non Hodgkin's lymphoma development in those treated with CsA has prevalence 28 times higher than the general population (Cockburn and Krupp 1989). Compared with NHL developing after non-CsA immunosuppression, CsA lymphoma develops sooner, has a different presentation (more often involving lymph nodes and small intestine, rarely involving the brain) and was more likely to regress after reduction of immunosuppressive therapy (Cockburn and Krupp 1989). Kirby et al (2002) reported a case of cutaneous T cell lymphoma development following low dose CsA therapy initiated for atopic eczema. The tumor resolved on cessation of therapy. Koo et al (1992) reported the development of a B-cell lymphoma following 8 months of CsA use (at a dose of less than 5 mg/kg/day), which was prescribed for recalcitrant psoriasis. The tumor presented 7 months after discontinuation of the treatment.

Other reports

Other reports have found that CsA use is associated with the development of malignancies and pre-malignant conditions throughout the body. Several authors (Seshadri et al 2001; Malouf et al 2004) have detailed the incidence of cervical intraepithelial neoplasia and papilloma infection in immunosuppressed patients in general. There is only a single case report (Grossman et al 1996) of cyclosporin mentioned specifically, however patients with uveitis do tend to be young and may be sexually active so this may be of particular concern. Ter Haar-van Eck et al (1995) did report that the incidence of abnormal cytology from smear testing in cyclosporin treated patients may be less than in more conventionally immunosuppressed patients.

Weinstein et al (2001) reported upon 5 patients who developed breast fibroadenomata following post-transplant CsA use, with an average dose of 265 mg/day for an average of 67 months. Similarly, Caetano Stefenon et al (2002) also reported the development of multiple, benign mammary nodules in an immunosuppressed patient on CsA. Piepkorn et al (1993) reported a case of Buschke-Lowenstein penile carcinoma associated with intermittent CsA therapy for pustular psoriasis. There are also reports of conjunctival epithelial neoplasia (Macarez et al 1999), tonsillar carcinoma (Swoboda and Fabrizii 1993), laryngeal carcinoma (Namyslowski et al 1994) and genitourinary carcinomata (Maung et al 1985; Schmidt et al 1995) attributable to CsA use.

Studies showing no increased risk of malignancy development with CsA use

Caillard's (Caillard et al 2005) study of 25,127 post-transplant patients with respect to PTLD development revealed that overall, 1.4% of the cohort developed NHL. When compared to those patients taking Tacrolimus, CsA treated patients had a lesser risk of developing the disease ($p = 0.02$).

Van den Borne (1998) performed a retrospective cohort study of Rheumatoid Arthritis (RA) patients who received CsA in the Netherlands between 1984 and 1995. They matched each of the 208 patients enrolled in the study with 2 control groups who had never received CsA. The findings suggested that CsA treatment in RA patients does not increase the risk of malignancies in general or of lympho-proliferative malignancy or skin cancers in particular. These results have been questioned as the trial was open to significant selection and assembly bias: only the index patients were thoroughly examined for pre-existing malignancy and the control group came from a different geographical area to the index cases.

Gruber (1994) compared the incidence of tumors developing in 1165 primary adult renal transplant recipients treated with a combination of azathioprine, prednisolone and antilymphocyte globulin with 722 patients receiving CsA as part of combined therapy. There was no significant difference in the overall incidence of cancer ($p = 0.41$) or skin cancer ($p = 0.97$). Non-CsA-treated patients demonstrated a *higher* incidence of lymphoma ($p = 0.05$). They did report that the mean time to cancer occurrence was significantly shorter in those patients who had been treated with CsA but

immunosuppressive regimen was not found to be a significant independent prognostic indicator for cancer development. Indeed D'Costa et al (2003) recently reported that CsA *inhibits* the growth of a variety of lymphoid tumors in vitro, particularly in combination with irradiation.

London's (London et al 1995) long term retrospective analysis of renal allograft patients, revealed that 70 out of 918 patients developed a malignancy following transplant and subsequent immunosuppression. There was no evidence to support that there is an increased risk of cancer with CsA treatment over other immunosuppression regimes. It was conceded however, that the patients treated with CsA had a much shorter follow-up period.

Ophthalmic uses of systemic CsA and the risk of neoplasia

Patients suffering scleritis, Behçets disease, birdshot retinochoroidopathy, pars planitis, sarcoidosis, Vogt-Koyanagi-Harada (VKH) syndrome and sympathetic uveitis have all been successfully treated with systemic CsA. CsA has also been used to prevent corneal transplant rejection in high risk cases. Orsoni et al (2004) advocates the treatment of congenital syphilitic keratitis with CsA at a dose of 4 mg/kg/day (in combination with low dose steroid).

The majority of evidence in the non-ophthalmic literature shows that CsA causes malignancy and this is now a widely accepted risk – so how do we translate this to our ophthalmic practice? Many studies report the use of CsA in ophthalmology but few mention the development of malignancy in their cohorts.

Young et al (2002) reported an interventional case series, which randomised patients with acute corneal graft rejection into one of two groups concerned with the dose of CsA in conjunction with topical steroid and intravenous methylprednisolone. They found that a low dose CsA regime was less effective in reversing the rejection episode and there was no report of any malignancy development. A similar study by Poon et al (2001) with respect to prevention of rejection in high risk keratoplasties also did not show any malignancy development but they did conclude that CsA did not give a significantly increased benefit over conventional therapy in this situation.

Wakefield and McCluskey (1991) reported a study of 22 patients with sight threatening uveitis whose disease had previously been refractory to treatment. Nineteen patients showed significant clinical improvement after initial treatment with CsA. Side effects were common with doses greater than 5 mg/kg/day. Muftuoglu et al (1987) reported improvements in Behçets disease – both ocular and mucocutaneous symptoms – using an oral dose of 10 mg/kg/day with similar side effects. Neither studies commented upon any malignancy development with the treatment. Nussenblatt et al (1985) reported long term follow up of 52 uveitis patients treated with CsA and specifically reported "….We did not observe opportunistic infections nor CsA associated neoplasms in our patients." Vitale et al (1996) reported on 92 eyes with uveitis of various etiologies that had been treated with low-dose CsA (2.5–5.0 mg/kg daily) alone or in combination with prednisolone and/or azathioprine. The CsA was discontinued in five patients due to nephrotoxicity, systemic hypertension or constitutional intolerance to the drug. Again there was no mention of any malignancy development.

There are two case reports of malignancy developing following CsA use in an ophthalmology patient; the development of a malignant rhabdoid tumor in a patient treated with CsA for Behçets disease (Muramatsu et al 1998) and a patient who developed a gastric Epstein-Barr virus induced B-cell lymphoma following systemic CsA treatment, which was initiated as prophylaxis for a high risk keratoplasty (Algros et al 2002).

Topical cyclosporin

In any type of ocular surface disease a downward spiral of increasing inflammation and damage is present, meaning topical CsA may be an effective alternative to topical steroids in these conditions. Although topical CsA has been investigated and reported since the 1980's, due to problems with sterility, pH, particles and its inherent lipophilia only recently has a commercially available product been made available (Restasis, cyclosporine ophthalmic emulsion 0.05%, Allergan Inc).

The early study showed that topical 2% cyclosporin penetrated the aqueous to noticeable levels but without detectable levels in the serum (Diaz-Llopas and Menezo 1989). This has been contradicted by Zhao and Jin (1993) who showed that small amounts of CsA were found in the blood following the use of 0.5% CsA. This is the only report of blood serum levels of CsA being elevated and current animal studies show that systemic absorption is negligible (TangiLiu and Acheampong 2005).

The main indication for topical CsA is for relief of dry eyes due to a combination of its immunomodulatory effects and possibly direct lacrimogenic effects. Topical CsA is also advocated for the use in; atopic and vernal keratoconjunctivitis, Thygeson's superficial punctate keratitis, ligneous

conjunctivitis and conjunctival involvement with lichen planus (Holland et al 1993; Tatlipinar and Akpek 2005).

There are a wealth of studies relating to studies of the safety and efficacy of topical CsA however, there are no reported cases of malignancy associated with the topical formulation. We would expect that local administration of CsA to have low risk of systemic tumor development due to the negligible absorption. In contrast to the report of conjunctival neoplasia development following systemic CsA (Macarez et al 1999), a recent report (Tunc and Erbilen 2006) advocates the use of topical CsA (in conjunction with Mitomycin C) for the *treatmen*t of ocular surface squamous cell carcinoma.

Comparison of malignancy potential of CsA with other immunosuppressants used in ophthalmology

Other T-cell/calcineurin inhibitors

T-cell inhibitors have long been linked with post transplant malignancies. Tacrolimus has a similarly complex oncogenesis to cyclosporin. In murine models it has been shown to cause a 5-fold increase in lymphoproliferative disease in association with persistent herpes viral infection, to induce apoptosis in transgenic models studying Fas/Fas ligand interactions, and to induce TGF-β expression. Conversely it has been shown to inhibit intercellular adhesion molecules and thus prevent angiogenesis in cell culture. Although initial high relative risks of lymphoproliferative disease were reported with tacrolimus use, these were later attributed to inexperience with the agent and overaggressive dosing. A cohort study of children with post-transplant lymphoproliferative disorder (PTLD) compared to those without, found tacrolimus (in combination with mycophenolate) was not a risk factor in its development (Dharnidharka et al 2002) and it is argued to be safer than cyclosporin (Reichenspurner 2005).

Antimetabolites

Antimetabolites, particularly azathioprine have long been associated with a wide variety of neoplasms. The age-adjusted relative risk of developing any malignancy with its use has been calculated at 0.85 in multiple sclerosis patients (Amato et al 1993). A cohort study of 1000 renal transplant recipients reported patients on azathioprine had a lower cumulative incidence of tumors than those on CsA regimes (McGeown et al 2000), however the increased risk of nonmelanotic skin malignancies (particularly squamous cell carcinoma) posttransplantation is largely thought attributable to azathioprine use (Kasiske et al 2004). Although there have been an increasing number of case reports of lymphoma in rheumatoid arthritis patients treated with methotrexate, some with spontaneous remission upon treatment cessation, a large prospective study failed to establish a causal relationship (Wolfe and Michaud 2004).

Alkylating agents

Most of the data supporting the increased malignancy potential of alkylating agents has been in conditions with intrinsic malignancy risk. However in a randomized controlled trial of 431 patients with polycythaemia vera, the rate of acute leukaemia was 13.5-fold greater with chlorambucil treatment than with phlebotomy or radioactive phosphorus and appeared to be dose related (Berk et al 1981). A case-controlled study of 238 patients with rheumatoid arthritis attributed a 1.5-fold increase of bladder, skin and myeloproliferative malignancies with cyclophosphamide use (Radis et al 1995). This effect was associated with longer duration of treatment, and in the case of bladder cancer appeared to be long-term.

Anti-TNF therapy

Tumor necrosis factor (TNF) is important in natural killer cell and CD8 lymphocyte-mediated destruction of tumor cells, however conversely tumor promoting effects of TNF have also been described. Anti-TNF antibody therapy has been linked in particular to basal cell carcinoma and lymphoma. A meta-analysis of randomized trials of rheumatoid arthritis patients comparing infliximab and adalimumab treatment versus placebo calculated a pooled odds ratio for malignancy of 3.3 times higher in the anti-TNF group compared with the control group, with a dose-dependent relationship (Bongartz et al 2006). A prospective cohort study of rheumatoid arthritis patients suggested an increased risk of lymphoma in those receiving anti-TNF therapies over methotrexate or no disease-modifying drugs. The standardized incidence ratio was higher with etanercept than infliximab although differences were slight and confidence intervals overlapped (Wolfe and Michaud 2004). Etanercept was recently statistically significantly linked to solid tumors but not to basal or squamous cell carcinomas in a randomized trial of patients with Wegener's granulomatosis comparing etanercept plus cyclophosphamide therapy to cyclophosphamide alone (WGET Research Group 2005).

In contrast, newer immunosuppressive agents such as mycophenolate and sirolimus appear to have antiproliferative properties. This has been demonstrated with mycophenolate

against leukaemias and lymphomas both in vitro and in vivo and in colon and prostate carcinoma cells. The agent has been shown to suppress glycosylation and expression of several adhesion molecules key to solid tumor dissemination, and to inhibit adhesion of colon adenocarcinoma cells to endothelial cells. These properties are expressed in population analyses of transplant recipients where mycophenolate has a protective effect within immunosuppression regimes (Cherikh et al 2003; Dharnidharka et al 2002). Indeed higher doses of mycophenolate confer lower relative skin cancer risk (Wang et al 2004). Similarly, sirolimus (rapamycin) has remarkable antineoplastic properties, with reduced incidences of malignancies both alone and in combination with CsA/tacrolimus in transplant recipients (Kauffman et al 2005; Kreis et al 2004). It has also been shown to induce resolution of Kaposi's sarcoma (Stallone et al 2005).

Comment and recommendations

Many of the studies used to formulate this review have been limited by their design and study population. The majority of studies have been retrospective, specific to their speciality, mainly with renal transplant patients. Although it is difficult to extrapolate the findings of these studies to ophthalmic practice, two key issues emerge. The most striking feature that is evident is that the rate of neoplasia increases with duration of treatment and follow-up. Secondly, there appears to be a relationship between the dose of CsA used and the development of malignancy (Cockburn and Krupp 1989; Arellano and Krupp 1993; Farge 1993; Dantal et al 1998; McGeown et al 2000).

Although there are scarce reports of malignancy following CsA use in ophthalmic practice, all of the studies regarding CsA use in ophthalmology have been concerned with clinical outcome rather than development of malignancy. The doses of CsA used in ophthalmic practice are in the same range as many of the studies reporting significant malignancy rates, but the treatment time and, importantly, the follow-up times have been much less.

What is required is a cohort study of CsA use in ophthalmic disease with particular reference to the development of malignancy. Only then can the full risks be weighed against the benefits of CsA. The rate of tumor development with prolonged CsA should be of concern to the ophthalmic community. After thorough examination of the published literature, we propose some recommendations for the assessment of patients who are to be considered for treatment with CsA.

Recommendations

1. Relative contraindications to the use of CsA should include current or past skin malignancy (except for basal cell carcinoma) and lymphoproliferative disease. A history of remote malignancy should be treated as a cause for concern.
2. Premalignant conditions such as leukoplakia, monoclonal paraproteinaemia and myelodysplastic syndrome should be excluded.
3. Before commencing treatment with CsA, patients should be examined for skin malignancy (for SCC and KS) and screened for potential lymphoproliferative disease by enquiring for suggestive symptoms and examination for lymphadenopathy and hepatosplenomegaly.
4. Whilst undergoing therapy, monitoring should continue for the development of skin tumors and lymphoproliferative disorders.
5. The presentation of lymphoproliferative disorders can range from tonsillar hyperplasia to frank nodules of internal organs or lymph nodes, in addition, the development of suspicious symptoms such as fever, night sweats and substantial weight loss would warrant further investigation.
6. Full investigation for lymphoproliferative disease includes computerised tomography (CT) of the chest, abdomen and pelvis and this should be performed if the diagnosis is suggested.
7. Self-monitoring by the patient is also clearly important and should be encouraged.
8. Patients should be advised to use a sun screen when exposed to the sun.
9. Although CsA related malignancy tends to be either of skin or the lymphoproliferative system it should be remembered that other malignancies can develop. Routine screening, especially cervical screening, should be enforced rigorously.
10. The use of condoms should be actively encouraged in the sexually active patient.
11. The development of malignancy attributable to CsA can present following discontinuation of its use, so arrangements for follow-up examination should be made for at least 5 years.
12. The use of minimal effective dosages may reduce the carcinogenic potential of CsA.

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