Post-transplant Skin Cancer and Immunosuppressive Therapy Regimens

Petter Jensen Gjersvik
P.O. Box 1152 Sentrum, NO-0107 Oslo, Norway.
petter.gjersvik@legeforeningen.no

Summary

The risk of cutaneous squamous cell carcinoma (SCC) after organ transplantation is related to the degree and duration of long-term immunosuppression. Although the risk may be expected to increase with new and more powerful immunosuppressive drugs or drug combinations, it is possible that non-carcinogenic immunosuppressants may be developed.

Several well-performed epidemiological studies have documented a marked increased incidence of SCC in organ transplant recipients, compared with that in the general population (1–4). The risk for basal cell carcinoma (2) and Kaposi's sarcoma (3), and possibly also for malignant melanoma (3), is also increased, but this is not as important as the increased risk for SCC.

The main cause of SCC, both in organ transplant recipients and in the general population, is sun exposure. Ultraviolet radiation from the sun causes DNA damage, but normally such DNA alterations will be repaired or the cell will die through apoptosis. p53 probably plays an important role in DNA repair. Failure to repair UV-induced DNA alterations due to a dysfunctional p53 protein will lead to unrestrained cell proliferation and ultimately tumour formation (5).

Within a transplant cohort, age, light skin type and greater sunlight exposure are significant risk factors for developing SCC (1). It is still uncertain whether human papillomavirus plays a role in post-transplant skin cancer, and reports that some HLA types are over- or under-represented in kidney transplant recipients with skin cancer have not been confirmed.

The increased incidence of skin cancer is attributed to the immunosuppressive therapy, either by the immunosuppression per se or by non-immune mechanisms. An important question is therefore: Is one immunosuppressive drug or drug regimen more carcinogenic than others?

Therapy regimens in organ transplantation

The immunosuppressive drugs used in organ transplantation have different mechanisms of action (7). Azathioprine is a purine analogue and inhibits purine metabolism by being incorporated into cellular DNA. Cyclosporine acts through an inhibition of calcineurin, suppressing interleukin 2 production and T- cell proliferation, and has since its introduction around 1983 been the cornerstone of the immunosuppressive regimen at most transplantation centres. Later, other important immunosuppressive drugs have been introduced, such as tacrolimus, mycophenolat mofetil (MMF), rapamycin, and others. Tacrolimus is a calcineurin inhibitor, like cyclosporine, and is primarely used in liver transplantation, but increasingly also in other forms of organ transplantation. MMF inhibits cell proliferation very much like azathioprine and has replaced azathioprine in many transplantation centers.

Rapamycin and the rapamycin-analogues sirolimus and everolimus have different mechanisms of action than the drugs previously mentioned, and may come in wider use in organ transplantation in the future.

High doses of systemic steroids are given the first weeks after transplantation and against acute graft rejection. Most transplant recipients also receive a low dose prednisolon as maintenance therapy. In the first days or weeks post-transplantation, some patients have received polyclonal antibodies against human lymphocytes or, more recently, monoclonal antibodies against a defined T-cell antigen, often referred to as induction therapy.

Different risk with different regimens

An increased risk for non-melanoma skin cancer in transplant recipients was reported in the 1970's when azathioprine and prednisolone was the only drug regimen available. The first reports in the late 1980's and early 1990's could not conclude whether cyclosporine and prednisolone with

or without azathioprine increased the risk of skin cancer more than azathioprine and prednisolone did. Bouwes Bavinck et al. (7) reported in 1991 no relation between the risk of skin cancer and induction therapy, or with the number of rejection treatments. This indicated that intensive immunosuppression given for a short time is not important for the development of post-transplant skin cancer.

In 1997, Glover et al. (8) reported that a cohort of 180 kidney transplant recipients on cyclosporine, azathioprine and prednisolone had a 8.4 times higher risk of SCC compared to a historical group of 82 recipients on azathioprine and prednisolone. The fact that the risk of basal cell carcinoma was similar in both groups, indicated that the increased risk of SCC was not a result of improved clinical surveillance. In a population-based study from Norway, a cohort of nearly 1900 kidney transplant recipients immunosuppressed with cyclosporine, azathioprine and prednisolone had a 4.2 times higher risk of SCC than a historic group of nearly 800 recipients on azathioprine and prednisolone (3).

That cyclosporine is more carcinogenic than azathioprine could be due to a better and more effective immunosuppression by cyclosporine, as transplant and recipient survival is significantly better with than without cyclosporine. Cyclosporine has a more specific effect on T cells than azathioprine. Another explanation is that the difference is related to a direct drug effect. In a randomised prospective study in France, the incidence of post-transplant skin cancer was related to the dose of cyclosporine (9). In 1999, Hojo et al. (10) reported that cyclosporine may promote lung tumour growth in mice independently of its effect on the host immune system, but is uncertain whether this has relevance for human epidermal neoplasia. In 2001, Herman et al. (11) reported a dose-dependent reduction in DNA repair in blood mononuclear cells by cyclosporine, and that cyclosporine reduced DNA repair ability more than azathioprine did.

More interesting than comparing cyclosporine with azathioprine is comparing cyclosporine with newer immunosuppressive drugs, like tacrolimus, MMF, rapamycin and others. It is well documented that regimens with tacrolimus and MMF increase the risk of SCC, but to what extent or, more specifically, whether the risk of post-transplant skin cancer with such regimens is higher than with cyclosporine-based regimens, is simply not known. No well-performed clinical or epidemiological studies have been performed to answer this question.

Rapamycin inhibits tumour angiogenesis and metastatic growth in mice (12) and blocks the progression of renal tumour growth and metastatic progression in severe combined immunodeficient mice regardless of cyclosporine-induced immunosuppression (13). It has also been reported that rapamycin inhibits several UV-induced mechanisms involved in skin carcinogenesis (14). These are very promising findings, although the effect of rapamycin on human skin carcinogenesis in clinical practice is unknown (14).

So the dogma still remains, but is now being challenged: The risk of post-transplant skin cancer, i.e. SCC, is related to the degree and duration of long-term maintenance immunosuppression and must be expected to increase with new and more powerful immunosuppressive drugs or drug combinations. It is possible, however, that non-carcinogenic immunosuppressive drugs may be developed, and that acute and chronic rejection of a transplanted organ may be prevented by other means than by the use of immunosuppressive drugs.

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