1.Introduction

Renal transplant patients on maintenance immune-suppression have a long term increased risk of malignancy. When malignancy develops consideration must be given to modification of the immunosuppressive regimen by dose reduction or changes in the drugs used.
The increased malignancy risk in renal transplant patients appears to relate to the long term requirement for maintenance immune-suppression interfering with “immune surveillance” of pre-malignant cells. There is no consistent evidence that particular immunosuppressive drugs are associated with additional increased risk of malignancy. Cumulative duration of immune-suppression is the strongest predictor of risk.
Recent data suggest that the use of sirolimus is associated with reduced risk of recurrent skin malignancy. There are as yet insufficient data on the use of sirolimus in renal transplant patients with other malignancies to justify changes in clinical practice..
The common practical clinical question is whether reduction of maintenance immune-suppression can significantly improve outcome for the malignancy without Compromising graft function.

2.Scope

This guideline is to help medical, nursing and pharmacy staff managing patients undergoing renal transplantation who develop malignancies.
This guideline makes broad recommendations for three groups of patients:-

- Patients who develop a post-transplant lymphoproliferative disorder or lymphoma.
- Patients who develop non-melanoma skin cancer
- Patients who develop epithelial malignancy

Clinical guidelines are ‘guidelines’ only. The interpretation and application of clinical guidelines will remain the responsibility of the individual practitioner. If in doubt consult a senior colleague or expert.

3.Recommendations, Standards and Procedural Statements

3.1 Post-transplant lymphoproliferative disorder and lymphoma

The risk for these conditions remains increased (approximately 10-fold) throughout the period of transplantation. The highest risk is for post-transplant lymphoproliferative disorder (often EBV driven) in the first 12 months after transplantation. The risk of PTLD has significantly increased over recent years with more intensive induction and maintenance immunosuppressive regimens. Risk is increased by EBV status which is presently documented for transplant donors and recipients but not used to influence transplant decisions.

All patients will PTLD and lymphoma will be managed in close collaboration with the Department of Haematology. Decisions to change immunosuppression will be made in direct liaison with them.

3.1.1 Post-transplant lymphoproliferative disorder

- Usual management will be immediate reduction or withdrawal of calcineurin inhibitor and withdrawal of mycophenolate. Low-dose corticosteroid treatment – typically prednisolone 10mg to 20mg daily - is continued.
- A biological anti-B cell agent, e.g. Rituximab, may be indicated
- If remission is achieved, low-dose calcineurin inhibitor is usually introduced three to six months later if graft function is stable. Low normal trough levels should be maintained after re-introduction– targets: tacrolimus 5mg/ml, ciclosporin 50mg/ml.
- If graft function has deteriorated severely, a decision may be made not to introduce immunosuppression but to accept graft loss.
- If the patient is re-transplanted after PTLD, there is no evidence that altering the initial immunosuppressive regimen will influence the risk of recurrence.

3.1.2 Lymphoma

- Lymphoma other than PTLD is much more heterogeneous in the renal transplant population. Management will be decided on a case-by-case basis in liaison with haematology. Chemotherapy as well as reduction in immunosuppression and/or rituximab is usually required.
- During chemotherapy mycophenolate is withdrawn; calcineurin inhibitor dosage is halved; low-dose prednisolone is maintained.
- Following chemotherapy maintenance immunosuppression may be increased to previous levels over three to six months.

3.2 Non-Melanoma Skin Cancer

Non-melanoma skin cancer [both squamous and basal cell carcinoma] is very common in renal transplant patients as the risk is cumulative. The main transplant-specific factors are the duration of immunosuppression, the choice and use of individual immunosuppressive agents is not proven to increase risk. Azathioprine has commonly been implicated because it is the immunosuppressive agent with longest experience, but this drug gives no higher risk than other immunosuppressives. 2% of all deaths in renal transplant recipients are due to metastatic squamous cell skin cancer (SCC) (this is more than deaths due to PTLD).

A small RCT from Germany indicates that the introduction of sirolimus reduces progression of pre-malignant skin lesions and de novo cancers in long standing renal transplant recipients. Two other RCTs of the introduction of sirolimus to reduce risk of recurrent SCC have recently been completed and await peer-reviewed publication. Preliminary data of one trial are in the public domain and indicate a significant reduction in recurrence risk.

- Therefore, <u>all renal transplant recipients who develop a biopsy-proven skin SCC should be offered a switch to sirolimus</u>. Sirolimus should be started at 3mg daily with low target trough blood levels (5ng/ml). Calcineurin inhibitor (tacrolimus or ciclosporin) and anti-metabolite (azathioprine or mycophenolate) should both be withdrawn immediately. Prednisolone 5mg daily should introduced in patients not on maintenance corticosteroids. (*This regimen is used in the Oxford Renal Transplant Unit by Dr. P Harden, principal investigator for one of the RCTs).*
- If a patient chooses not to switch to sirolimus, there is no evidence that modifying calcineurin inhibitor, azathioprine or mycophenolate dosage alters the natural history of the skin disease.
- If a patient continues on a calcineurin inhibitor, the dosage should be adjusted to maintain levels at the lower end of the therapeutic range (tacrolimus 5mg/ml,

ciclosporin 50mg/ml) but there is no justification for reducing to sub-therapeutic dosage.

- Data indicates that conversion to sirolimus in patients with significant renal impairment (i.e. serum creatinine > 220µmol/L; eGFR <40mls/min) or significant proteinuria (> 800mg/day; PCR > 80mg/mmol)) is unlikely to prevent ongoing allograft failure. Therefore conversion should be undertaken before significant renal impairment develops. Sirolimus conversion has been associated with significant increases in proteinuria. Therefore patients with heavy proteinuria (>1g/day) should probably not be considered suitable for conversion to sirolimus.(For information about sirolimus in renal transplant patients see 'Sirolimus conversion in the renal transplant recipient guideline').
- In Kaposi"s sarcoma there is substantial anecdotal evidence that sirolimus may allow tumour regression in some cases. The decision to switch to sirolimus will be made on a case-by-case basis

3.3 Other Epithelial Cell Malignancy

Risks for renal transplant patients developing these malignancies are two to four times the general population. These cancers occur in renal transplant patients most often in those sites common in the general population (for example breast, lung, colon, kidney, pancreas)
There is no evidence that modifying immunosuppressive dosages alters the natural history of patients either in altering the risk of metastasis or in changing the rate of progression once metastatic disease has developed. Nor is there evidence that immunosuppression modifies the response to treatment which should be along conventional lines with surgery, chemotherapy and radiotherapy as indicated by the oncologist in charge of the case.

When intensive chemotherapy regimens are used it may be appropriate to maintain low dose corticosteroids, reduce calcineurin inhibitor dosage, and discontinue other agents during chemotherapy and for up to three months afterwards. This will be decided on a case-by-case basis.

3.4 Level of clinical decision making

All decision to modify immunosuppressive regimens because of malignancy must be discussed with a consultant nephrologist and, in the first twelve months after transplantation, also with a consultant transplant surgeon.

4.**Education and Training**

None required

5.**Monitoring and Audit Criteria**

Key Performance Indicator	Method of Assessment	Frequency	Lead
Audit of malignancies in renal transplant patients	Retrospective audit	Ad hoc	Transplant nephrologists

6.Legal Liability Guideline Statement

See section 6.4 of the UHL Policy for Policies for details of the Trust Legal Liability statement for Guidance documents

7.Supporting Documents and Key References

Feng S, Buell JF, Chari RS, et al. Tumors and transplantation: the 2003 third annual ASTS state-of-the-art winter symposium. Am J Transplant. 2003; 3(12): 1481-1487.

Trofe J, Buell JF, Beebe TM, et al. Analysis of factors that influence survival with post-transplant lymphoproliferative disorder in renal transplant recipients: the Israel Penn International Transplant Tumor Registry Experience. Am J Transplantation. 2005; 5: 775-780.

Ho M, Miller G, Atchison RW, et al. Epstein-Barr virus infections and DNA hybridization studies in posttransplantation lymphoma and lymphoproliferative lesions: the role of primary infections. J Inf Dis. 1985; 152: 876-886.

Caillard S, Dharnidharka V, Agodoa L, et al. Posttransplant lymphoproliferative disorders after renal transplantation in the United States in era of modern immunosuppression. Transplantation. 2005; 80 (9): 1233-1243.

Nepomuceno RR, Balatoni CE, Natkunam Y, et al. Rapamycin inhibits the interleukin 10 transduction pathway and the growth of Epstein-Barr virus B-cell lymphomas. Cancer Res. 2003; 63(15): 4472-4480.

Trofe J, Buell JF, Beebe TM, et al. Analysis of factors that influence survival with post-transplant lymphoproliferative disorder in renal transplant recipients: the Israel Penn International Transplant Tumor Registry Experience. Am J Transplantation. 2005; 5: 775-780.

Euvrard S, Ulrich C, Lefrancois N. Immunosuppressants and skin cancers in transplant patients: focus on rapamycin. Dermatol Surg. 2004; 30: 628-633.

Mathew T, Kreis H, Friend P. Two-year incidence of malignancy in sirolimus-treated renal transplant recipients: results from five multicenter studies. Clin transplant. 2004; 18: 446-449.

Salgo R, Gossmann J, Schöfer H, Kachel HG, Kuck J, Geiger H, Kaufmann R, Scheuermann EH. Switch to a sirolimus-based immunosuppression in long-term renal transplant recipients: reduced rate of (pre-malignancies and nonmelanoma skin cancer in a prospective, randomized, assessor-blinded, controlled clinical trial. Am J Transplant. 2010 Jun;10(6):1385-93. Epub 2010 Feb 1.

Harden P et al. The RESCUE trial Transplant International 2011 (abstract) in press

8.Key Words

Renal transplant; immunosuppression; lymphoma; lymphoproliferative disorders; skin cancer; calcineurin inhibitors

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5-Oct-11	2	J Feehally	Update with new data on sirolimus in skin malignancy
10-Feb-17	3	S Carr	Updated on new proforma Included information re sirolimus conversion