

## Chapter 20: Managing Cancer with Reduction of Immunosuppressive Medication

**20.1: We suggest consideration be given to reducing immunosuppressive medications for KTRs with cancer. (2C)**

**20.1.1: Important factors for consideration include (Not Graded):**

- the stage of cancer at diagnosis;
- whether the cancer is likely to be exacerbated by immunosuppression;
- the therapies available for the cancer;
- whether immunosuppressive medications interfere with ability to administer the standard chemotherapy.

**20.2: For patients with Kaposi sarcoma, we suggest using mTORi along with a reduction in overall immunosuppression. (2C)**

**KTRs, kidney transplant recipients; mTORi, mammalian target of rapamycin inhibitor(s).**

### Rationale

- In KTRs, cancers that have a high or moderately increased SIR (e.g.  $\geq 3.0$ ) are likely caused or exacerbated by immunosuppressive medication.
- In KTRs that develop cancers likely to be caused or exacerbated by immunosuppressive medication, reducing immunosuppressive medication may prolong survival.
- In KTRs, cancers that have a low SIR (e.g.  $\leq 1.5$ ) are unlikely to have been caused or to be exacerbated by immunosuppressive medication.
- In KTRs that develop cancers that are unlikely to be caused or exacerbated by immunosuppressive medication, reducing immunosuppressive medication is less likely to have a significant effect on survival, and may increase the risk for acute rejection.
- Reduced quality of life from graft loss must be balanced against the potential for prolonging survival by reducing immunosuppression.
- Reducing immunosuppressive medications may reduce complications of cancer chemotherapy.
- In KTRs with Kaposi sarcoma, dramatic reductions in lesion size have been associated with a change in immunosuppressive medication to mTORi.

In KTRs, non-renal cell cancers that have a high SIR (e.g.  $\geq 3.0$ ) are likely caused or exacerbated by immunosuppressive medication. There is strong evidence that immunosuppressive medication increases the risk of some specific types of cancer, notably cancer that may be caused by viruses (Table 30). There is little evidence that specific immunosuppressive agents are more likely than others to increase the risk of cancer. It is more likely that the total amount of immunosuppressive medication increases the risk for cancer, rather than the type of immunosuppressive medication *per se*. Observational data have suggested that there is an association between PTLD and the use of biological anti-T-cell agents (674). There is evidence from *post hoc* analysis of RCTs that there was a reduction in cancer incidence in sirolimus treatment arms (119,675). However, the numbers of patients developing cancer were small, and the *post hoc* nature of the analysis increases the possibility that the results were due to chance.

To reduce immunosuppressive medications in KTRs diagnosed with cancer is a difficult decision. There is evidence that the risk of *de novo* cancer returns to pretransplant levels after graft failure (676–679), suggesting that reducing immunosuppressive medication may be warranted. Experimental studies have demonstrated the specific capacity of CNIs to increase metastasis (680). Clinical studies have implicated antiproliferative agents in increased, and mTORi in relative reduction in cancer risk. However, there have been no RCTs testing the effects of reducing or withdrawing immunosuppressive medications in posttransplant cancer, and it is possible that established cancer and *de novo* cancer behave differently under the influence of immunosuppression. The standard established treatment for PTLD and Kaposi's sarcoma includes reducing immunosuppression, and this has proven to be sufficient to control or eliminate tumors in some KTRs (681).

The decision to reduce or withdraw immunosuppressive medication must also balance quality of life with and without a functioning transplant, if cessation of medication results in graft rejection. Altogether, evidence suggests that consideration should be given to reducing immunosuppressive medications in each individual, but since this evidence is weak, the type of cancer, stage of disease, and patient preferences should be taken into account.

In KTRs, cancers that have a low SIR (e.g.  $< 3.0$ ) are unlikely to be caused or exacerbated by immunosuppressive medication. In distinction to those cancers in which the SIR is elevated in immunosuppressed KTRs, cancers in

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**Table 30:** Viral-associated cancers

Virus	Malignancy site/Type of cancer	
	Sufficient evidence	Limited evidence
HBV and HCV	Liver	
Human T-cell lymphotropic virus type 1	Non-Hodgkin lymphoma	
Human Herpes virus 8	Kaposi sarcoma	
EBV	Nasopharynx, Non-Hodgkin lymphoma, Hodgkin lymphoma	
HPV	Tongue, mouth, tonsil, anus, vagina, cervix, penis	Nonmelanoma skin, larynx

EBV, Epstein-Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HPV, Human papillomavirus.  
Modified with permission (621).

which there is no evidence for an increased risk from immunosuppression have no rationale for reducing or ceasing therapy.

In KTRs who develop cancers that are unlikely caused or exacerbated by immunosuppressive medication, reducing immunosuppressive medication will likely have little effect on survival, and may increase the risk for acute rejection. There are no data to support or refute altering immunosuppression after development of cancer of the prostate, breast, ovary, uterus, pancreas, brain glioma or testis. However, many of the complications of cancer chemotherapy are also complications of immunosuppressive agents used in KTRs, and reducing immunosuppressive medications to prevent or treat complications of chemotherapy is warranted.

Several case series in patients with established Kaposi sarcoma have demonstrated benefits from conversion from standard immunosuppression to either sirolimus or everolimus. Cases with disease limited to the skin have had resolution of the skin lesions, while the responses of disseminated solid-organ invasive disease have been less convincing (682,683). The strong benefit seen in these case series, together with experimental data and a clear scientific rationale for efficacy through inhibition of vascular endothelial growth factor-F receptors, have lead to the conclusion that patients with Kaposi sarcoma should be immunosuppressed with these agents in preference. On the other hand, there are also case series that have shown regression of Kaposi's sarcoma with a reduction in immunosuppressive medication alone (684).