POST TRANSPLANT MALIGNANCY

KIDNEY TRANSPLANT

BACKGROUND

- Malignancy after transplant remains a major concern to overcome in post transplant. In fact, it is one of the most feared complications.
- It is second only to CV diseases as a leading cause of mortality after transplant (surpassing death from infection, overtaking CV diseases within the following years).
- Cancer is responsible for 8 to 10 percent of all deaths in KT.
- Knowledge of post transplant malignances may help to improve patients' survival after transplant and guide the development of an optimal screening and surveillance plan for them.

OVERVIEW

- Epidemiology and mortality incidence
- Risk factors for malignances
- Prevention and treatments
- Summary

INCIDENCE

- Cancer incidence in solid organ transplants is increased to 2-4 fold compared with the general population.
- Cumulative incidence vary from 5% during the first year to 15% after 10 years and >50% 25 years after the transplant.
- Increased risk is site specific with greatest risks incurring for immune driven and viral related cancers.
- The age of diagnosis of PT cancers is 40 and the time from transplantation is 3-5 years.
- The most common cancer after transplant is NMSC, however, the incidence and type of cancer differ depending on geographic and ethnicity.

Einollahi et al.

STANDARD INCIDENCE RATIO (SIR) OF POST – RENAL TRANSPLANT MALIGNANCY COMPARED TO THE GENERAL POPULATION

SIR to general population	**Post renal transplant malignancy**
>5	NMSC, PTLD, RCC, Lip, Kaposi sarcoma
2-5	Thyroid, Melanoma, MM, Leukemia
<2	Brain, Prostate, Lung

* Breast, Prostate

MORTALITY RATE

- Overall standardized mortality rates is 2-3 times higher than of the general population and the RR of death is higher among the youth and those with Melanoma, Anogenital and NHL.

- Elevated risk of cancer and cancer related deaths is exacerbated with repeated transplant and allograft losses.

- Malignancy is associated with an increased risk of all cause mortality, cancer specific mortality and of the development of de novo malignancy (Acuns et al.).

REASONS FOR THE POOR OUTCOMES

- Less response to treatment
- Acute rejection with the use of checkpoint inhibitors
- Presence of coexisting comorbidities
- Reduced kidney function
- Late presentation
- Aggressiveness of the malignancy

**Cancer drug dosing is challenging

RISK FACTOR FOR POST TRANSPLANT MALIGNANCIES

Patients related	Recipient age *Previous cancer Sun exposure *Viral infection Duration of dialysis
Transplant – related	Donor transmission Donor type Rejection
Medication related	*Net immunosuppression Induction therapy (OkT3, ATG) Maintenance therapy

VIRUSES ASSOCIATED WITH POST RENAL TRANSPLANTED MALIGNANCIES

Viruses	**Malignancy associated with virus**
EBV	PTLD, Smooth muscle tumor
BK (polyomavirus)	Urothelial carcinoma
HPV	Squamous cell carcinoma
HHV8	Kaposi sarcoma, Multiple – myeloma
HIV	Plasmablastic lymphoma, Merkle cell carcinoma
HCV	Hepatocellular carcinoma, Plasma cell neoplasm

*CMV

IMMUNOSUPPRESSION: INDUCTION THERAPY

- OKT3
- RATG
- IL – 2R antagonist
- Alemtuzumab

IMMUNOSUPPRESSION: MAINTENANCE THERAPY

- CNIS: cyclosporine and tacrolimus
- Anti- Metabolites: azathioprine and mycophenolate mofetil
- mTOR inhibitors
- Co-stimulation blocker: belatacept

**Cumulative immunosuppressive doses are vital

Immunosuppressant agent	Method of action	Role in carcinogenesis
Calcineurin inhibitor	Inhibition of IL-2 production through binding and inhibition of cyclophilin (cyclosporine) and FKBP-12 (tacrolimus), respectively	Production of TGF-β Production of VEGF Production of interleukin-6 (IL-6) (promotion of EBV-induced B-cell growth) Promotion of invasive behaviour of non-transformed cells Reduced ability to repair radiation-induced DNA damage Enhanced apoptotic effects of taxol and IFN-γ on human gastric and bladder cancer cells Increased rate of lymfoproliferative disorders in HSV-infected mice
Azathiopurine	Inhibition of DNA and RNA synthesis through incorporation of thiopurine analogues	Intercalation at the DNA level, inhibiting repair splicing and eliciting codon misreads Increased development of microsatellite DNA instability
Mycophenolate mofetil	Inhibition of inosine monophosphate dehydrogenase and *de novo* purine biosynthesis	Anti-proliferative effect on leukaemia and solid tumour Inhibition of adhesion molecules Suppressed glycosylation and expression of several adhesion molecules Inhibition of adhesion of colon adenocarcinoma cells to endothelial cells
mTOR inhibitors	Inhibition of mTOR pathway	Direct antitumour effect by inhibition of mTOR pathway Inhibition of angiogenesis Inhibition of p70 S6K: decreasing cancer cell proliferation Inhibition of interleukin-10: decreasing tumour cell JAK/STATs activity Inhibition of cyclins: blocking cell-cycle activity Decreased VEGF-A and VEGF-C signalling: impaired tumour angiogenesis Inhibition of growth signals in PTLD-associated EBV $^{+}$ B-cell lymphomas Inhibition of replication of EBV-positive B cells, T cells and NK cells Inhibition of ultraviolet B–induced metalloproteinase activation

ROLE OF THE IMMUNE SYSTEM IN CANCER SURVEILLANCE

- A: elimination, activation of the innate and adaptive immune cells and molecules to protect them from becoming tumor cells
- B: equilibrium phase, maintained in an immune-mediated latent period
- C: escape phase, tumor cells progress to clinical disease and/or metastasis

MECHANISMS OF CANCER IMMUNOSUPPRESSION

- Decreased immune surveillance
- Decreased antiviral responses
- Direct carcinogens effect

Thiazids diuretics

RECIPIENTS CANCER

- Active malignancy
  - They should be excluded from transplant.
  - Acceptable: indolent and low grade cancer
- Prior cancer
  - Low prospects for cure
    - Metastatic melanoma, advanced breast cancer
  - Curable cancer
    - Transplant is recommended but only after remission has been achieved and sustained for 2-5 years.

* Timing of KT after potentially curative treatments for cancer depends on cancer type and stage at initial diagnosis (decisions should be made collaboratively).

PREVENTION

- Vaccination
- Screening (pre and post transplant)
- Assessment of donor

TREATMENT

- Reduction of immunosuppression
  - Antimetabolite
  - CNIS inhibitors
- Conversion to mTORSi
  - NMSC
  - KS
  - RCC?

**Early steroid withdrawal

TREATMENT

- Surgical excision
- Radiation
- Chemotherapy
- Anti viral
  - PTLD, PCN, EBV associated SMT

SUMMARY

- Post transplant malignancy is the leading cause of morbidity and mortality.
- The risk is especially high for cancers associated with oncogenic viruses.
- The amount of immunosuppression and the type of drug used are very important in the risk of malignancy.
- Pre transplant malignancy is associated with worse outcomes after transplant.
- Some malignancies have modifiable risk factors, and it is important to know them.
- Timely screening, early detection and avoidance of modifiable risk factors and also effective treatments offer better outcomes.
- There is little consensus on the preventive measures; it seems that individualized prevention plans based on their risk factors and available screening tools should be the ultimate goal.

THE END

Thanks