TREATMENT OPTIMIZATION IN THERANOSTIC RADIONUCLIDE THERAPIES

WORLD CONGRESS IN MEDICAL PHYSICS AND BIOMEDICAL ENGINEERING
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The Content of my talk will includes 3 example vignettes

- 1. Radioiodine in thyroid cancer
- 2. Small peptides in neuroendocrine cancers
- 3. Antibodies in pediatric cancers
The maximum tolerated activity (MTA)

Bone marrow is the dose limiting for many radionuclide therapies

1) Blood clearance (beta dose)
2) Whole Body Clearance (gamma dose)


The use of $^{124}$I PET for thyroid lesion dosimetry

In XRT the treatment planner uses a CT (and other images) to determine the target volume defined by the radiation oncologist.

In XRT there are normal tissue constraints and so the planner must jostle with the beam directions and weights to optimize the plan.

In radionuclide therapy, the planner! studies the biodistribution and pharmacokinetics of a tracer quantity of the intended therapeutic.

In radionuclide therapy, there is no way to modulate the radionuclide distribution.

Or is there?
Restoring Radioiodine Uptake in Thyroid Cancer

A Paradigm Shift

New drugs are under development, such as selumetinib, that is a mitogen-activated protein kinase (MEK) inhibitor, that may restore the NaI symporter expression.

This can restore radioiodine uptake in metastatic thyroid cancer.
$^{124}$I-NAI PET: Building block for precision medicine in metastatic thyroid cancer

John Humm
Steve Larson (Contact PI)
Mike Tuttle
James Fagin
Alan Ho
Ravi Grewal
Keith Pentlow
Part 2 - Peptide Theranostics
Peptide Receptor Radionuclide Therapy (PRRT)

• There is been a recent explosion of interest in small molecule targeted therapies.
• Radiolabeled somatostatin receptor (sst) agonists, e.g. $^{177}$Lu-DOTATATE, have become an integral part of therapeutic management in patients with neuroendocrine tumors.
• These are ideal theranostic agents, where the molecular can be labeled with $^{68}$Ga for diagnosis and $^{177}$Lu for dosimetry and therapy.
Wolfgang Weber performed a head to head comparison of the radiolabeled sst antagonists $^{177}$Lu-JR11 against an sst agonist $^{177}$Lu-DOTATATE. A favorable tumor-to-organ dose ratios were found.

$^{68}$Ga-DOTA-JR11

Administered Activity: $4.4 \, \text{mCi (163MBq)}$

Acquired 60 min pi
3 min per bed
Q.clear recon (350)
**177Lu-DOTA-JR11**

Dosimetry Administration: 49 mCi (1.81 GBq)

**Projections for Therapy:**

Activity limits: 789 mCi (RM); 861 mCi (Kidney)

- 29 GBq
- 32 GBq

Index Lesion: 22 cGy/mCi

Lesion dose @ 200 mCi: 44 Gy

Lesion dose @ 789 mCi: 174 Gy
Part 3 - Antibody Theranostics
Long-lived $\beta^+$ emitting ($^{89}$Zr and $^{124}$I) radionuclides for ImmunoPET

- Required for imaging because of antibody kinetics
- Problematic for normal tissue dosimetry
Soon after injection all antibody is in the circulation - uninformative

- Slow clearance from circulation - metabolism/excretion and slow take up in target tissues – mostly uninformative
- Circulation continues to clear, ongoing take up in target tissues – informative but suboptimal
- Circulation almost clear - antibody distribution reaches “final” state – maximally informative

CRPC: $^{89}$Zr-anti-STEAP antibody: 185 MBq (5mCi)
Consequences for radiolabeled antibodies

- For solid tumors, even in the highest antigen density expressing tumors (CA-IX in renal cell carcinoma), radioimmunotherapy failed.

- So does it work or where might it work?

- We have seen such successive in radiosensitive tumors e.g. B-cell lymphoma (Bexxar and Zevalin)

How can we break out of this impasse?

- Intra-compartmental / intra-tumor administration
Intrathecal antibody therapy for leptomeningeal Disease
Pre-Therapy Dosimetry using $^{124}$I or $^{131}$I labeled Ab

Kim Kramer
Serial whole body $^{124}$I labeled Ab PET scans

- Ventricles
- Cervical
- Thoracic
- Lumbar

Perform ROI analysis on each of the 3 time point images:

- 4 hr
- 24 hr
- 48 hr
Recurrent neuroblastoma metastatic to the CNS


Radiolabeled antibodies added to conventional chemoradiation therapy may dramatically improve outcome in this disease.
Summary

• The management of patients with poorly differentiated metastatic thyroid cancer is undergoing a revolution due to the emergence of new targeted drugs that cause thyroid re-differentiation.

• The use of peptide theranostic agents is a remarkable success story in radionuclide therapies that will continue to grow and improve.

• Early hiccups in the field of radioimmunotherapy could have heralded the end of an era. However, new radiolabeled antibody theranostic agents are emerging that combine immunoPET ($^{89}$Zr, $^{124}$I) with therapy isotopes.

• The poor AUCs tumor/blood ratios (only 5 to 1 for macromolecular targeting agents) may be improved by intra-compartmental administration.

• This is a new era of personalized medicine where the quantitative capability of nuclear medicine may provide new therapeutic opportunities.