Toxicities of Diagnostic and Therapeutic Radiopharmaceuticals

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Don’t Confuse Radiation Absorbed Dose with Activity

- Activity - decays per second (Ci, mCi MBq)
- 1 Bq = 1 decay/sec 1 Ci = 3.7x10^{10} Bq
- Radiation Absorbed Dose - Energy deposited per unit mass of tissue (rad, Gy)
- Physician prescribes activity injected
- Dose to each organ determined by pharmacokinetics & biodistribution and can be calculated by dosimetry techniques
- Organ toxicity is determined by dose to organ
Radiation Toxicities

- **Low Dose** (diagnostics, diagnostic x-rays) Increased cancer risk
- **High Dose** (therapeutics, radiotherapy) cancer risk, early organ toxicity, late organ toxicity
- High dose may be $>1000 \times$ low dose
- Clinical data from high dose radiation comes mostly from External Beam Radiotherapy (XRT)
- **Early** toxicity occurs within days or weeks
- **Late** toxicity months to years post treatment
- Late toxicity is virtually unique to radiation
Diagnostic Radiopharmaceuticals

- low activity low dose

- Gamma emitters (gamma camera imaging) or Positron emitters (PET scanning)
- Provide images for diagnostic interpretation
- Concentrate in organs being imaged
- Usually sub-pharmacological mass doses (µg)
- Increased cancer risk is only expected concern
- Monitoring still needed to detect unexpected toxicity in clinical trials of new agents
Radiation Toxicity of Diagnostics

- Increase in cancer risk years after exposure
- Detectable only in large exposed populations
- Lifetime excess risk of cancer death $\approx 4 \times 10^{-4}$/rad
- Stochastic (random) effect: like a lottery
- Your chances of winning are small...but
- The more tickets you buy the better the chances
- If Jackpot is cancer you don’t want to win
- Dose As Low As Reasonably Achievable (ALARA)
Quantifying Risk

- To quantify risk you need a model
- Linear model usually assumed
- Risk is proportional to dose $R = C \times D$
- Supported by Hiroshima data
- Little or no data for doses $\leq 4$ rad
- Model extrapolates linear relationship to very low doses
- Is there a threshold for carcinogenesis?
Therapeutic Radiopharmaceuticals
High Activity High Dose

- Used for cancer treatment
- Concentrate in tumor being treated
- Beta emitters deposit energy locally in tumor
- Most also emit a gamma (dosimetry, imaging)
- Need high injected activity to produce high doses necessary for tumor control
- Similar doses to XRT
- Expect similar toxicities as XRT
Therapeutic radiopharmaceuticals

- Clinical experience with high dose radiation comes from external beam radiotherapy (XRT)
- Relation between dose and toxicity in an organ is non-linear with threshold (tolerance dose)
- Below threshold toxicity is rare
- Radiopharmaceutical tolerance doses may not be the same as for XRT
- Radiopharmaceutical organ doses calculated from serial gamma camera scan data (OLINDA)
Known Toxicities of High Dose Radiation

> 100 years clinical experience with XRT

- **Early Toxicity:** occurs soon after treatment
  Usually reversible when treatment stops
- **Late Toxicity:** delayed by months or years
  Usually irreversible and progressive
- Late toxicity-radiation link may be missed
- Early: bone marrow failure, skin reaction, GI
- Late: kidney or liver failure or spinal cord injury
- Late tox: each organ has a tolerance dose
- Kidney 23 Gy, liver 30 Gy, spinal cord 45 Gy
Small Molecules

- Free isotopes (I-131)
- Isotope chelates Y-90-DOTATOC
- Eliminated rapidly by glomerular filtration
- Short serum half life low WB dose
- High activity in the urine may deliver high doses to kidney and bladder
- Kidney and bladder toxicity has been reported in the literature with chelates
Treatment of neuroendocrine tumors

Moll et al Am J Kid Dis 37; 847-851 (2001)

Report on 29 patients

7 patients received >200 mCi/m²

5/7 developed late renal failure

22 patients received < 200 mCi/m²

None developed late renal failure

“Clean” cutoff between toxic and non-toxic doses when dosing in mCi/m²

83 multiple myeloma patients

Prescribed 20, 30 or 40 Gy to marrow + high dose chemo + BMT

7 patients in 40 Gy group developed late thrombotic microangiopathy of renal origin

5/7 died

27/83 developed hemorrhagic cystitis
Large molecules

- Radiolabeled monoclonal antibodies
- Zevalin, Bexxar approved for treating NHL
- Can’t pass through glomerular filter
- Stay in circulation for long time
- Deliver high whole body dose
- Bone marrow toxicity usually dose limiting
Special Cases: Pure Beta Emitters

- $^{90}$Y emits a $\beta$ but no $\gamma$
- Can not do dosimetry with $\gamma$ camera scans
- $^{86}$Y PET impractical in clinical setting
- $^{111}$In analogues may not accurately predict $^{90}$Y biodistribution or dosimetry
- If biodistribution varies from patient to patient, inability to perform individual patient dosimetry creates additional risk
Special Cases: Alpha Emitters

- Greater risk due to high RBE
- Rad for rad, 6 to 20 times the biological effect of gammas or electrons
- If no photon emitted same dosimetry problem as with $^{90}$Y
- If part of long decay chain must keep track of all radioactive daughters
Three Important Issues in the Design of Clinical Studies with Radiopharmaceuticals

1) Safety
2) Safety
3) Safety

Primum Non Nocere........Hippocrates

Thank You