Clinical Trials
Radiolabeled Drugs/Biologics
Radiation Dosimetry
Design, Methods, Limitations & Value in Safety Assessment

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Topics

• Code of Federal Regulations (CFR)
• Dosimetry – When to perform?
• Dosimetry trial design – therapeutic
• Outcome Correlation – Dose Limiting Toxicity
• Correlation Limitations
• Dosimetry & clinical trial safety design
• Cohort enrollment strategies
Dosimetry – Regulatory Authority
Code of Federal Regulations (CFR)
21CFR312.23(a)(10)(ii)

Radioactive Drugs: Collect sufficient data from
animal or human studies to allow a
reasonable calculation of radiation absorbed
dose to the whole body and critical organs
upon administration to a human subject.
Phase 1 studies of radioactive drugs must
include studies which will obtain sufficient
data for dosimetry calculations.
Goals for Dosimetry
(characterizational dosimetry)

• Estimate radiation exposures to all organs/tissues (MIRDOS 3/Olinda) for a typical individual for the specific radiolabeled drug/biologic

• Provide a “roadmap” of radiation exposures to monitor potential adverse events

• Dosimetry is not intended for prospective or retrospective “dose optimization”
Dosimetry
(characterizational dosimetry)

Current Limitations

• Dosimetry models/calculations are too variable between clinical sites
• Enrolled patient populations & organ tolerances/reserves too variable
  ➢ Pre-treatment chemotherapy & radiation therapy
  ➢ Naïve patient populations
Dosimetry
When to Perform?

Therapeutic radiolabeled drug or biologic
Minimum: First 6 subjects (2 cohorts of 3)
In initial Phase 1 MTD trial

Diagnostic radiolabeled drug or biologic
To be completed in Phase 1
Requirement to enter Phase 2
Therapeutic Radiopharmaceutical Trial Design

Phase I, First in human experience

Diagnostic – Biodistribution & Therapeutic

- $^{111}$In/$^{90}$Y
- $^{131}$I/$^{131}$I
Therapeutic Radiopharmaceutical Trial Design

Goal for First in Human MTD trial

Determine administered therapeutic dose -> Acceptable safety/toxicity profile

Appropriate Dose Models
- Total dose - mCi
- Weight - mCi/kg
- BSA - mCi/m²
Therapeutic Radiopharmaceutical Trial Design

Maximum Tolerated Dose (MTD)

Planned enrollment - Rationale & justification

• First cohort = “No effect” - Safety & Efficacy
• 5 – 6 cohorts of 3 subjects ->
  Dose Limiting Toxicities (DLT) ->
  Maximum Tolerated Dose (MTD)
Therapeutic Trial Design

First two cohorts (6 subjects)

- Whole body (WB) biodistribution images
  - Immediate
  - Daily x 5 or 8 days

- WB – ROIs - calculation MIRDOSE 3 (OLINDA) -> Organ and Tissue Dosimetry
Therapeutic Trial Design

- For each cohort (3 subjects)
  - Prior to therapeutic administration
    - Review, summarize, submit and discuss data
  - Administer therapeutic dose
MTD Outcome Correlation
Dose Limiting Toxicity (DLT)

Correlation

• Biodistribution & estimated organ dosimetry
• Monitored adverse events

NCI-CTC 2.0 -> 3.0
(National Cancer Institute -
Common Toxicity Criteria)
Correlation
DLT

Dose limiting toxicities (DLT)

- Grade IV hematologic for > 7 days
- Any Grade III non-hematologic
Correlation
DLT

Concepts

• Radiotherapeutic observed radiation dose at DLT -> end organ toxicity

• Total radiation dose for organs at DLT > acceptable organ radiation dose tolerance
Correlation

DLT

MTD Design
Dose limiting toxicity observed in 1 subject/1 organ

• Expand cohort from 3 to 6 subjects
• DLT 1/6 subjects -> next dose cohort
• If 2 subjects/any 2 organs with DLTs
  ➢ Close cohort to further enrollment
  ➢ MTD = Previous dose cohort
Correlation
DLT

For the reported organ dosimetry, the correlated MTD has been determined by any 2 end organ toxicities that are reversible

Hematologic
or
Non-hematologic
Limitations of dosimetry/MTD correlations

- Organ dosimetry is specific only to the radiolabeled therapeutic due to unique biodistribution of radiotherapeutic
- Organ dosimetry relatable only to target population & specific target population pre-treatment profile
- The therapeutic dose will not have produced adverse events (toxicity) in most organs
Correlation – Limitations

DLT

Radiation dosimetry relationship to MTD is based on

• limited toxicities of varied and possibly unrelated end organ radiation tolerances,
• in subjects with limited end organ reserves, due to existing disease and/or previous therapies
Correlation – Limitations

DLT

For the reported organ dosimetry

• A specific end organ, may not have experienced significant (Grade 3/4) toxicity
• Possibly only 1 or 2 subjects -> limiting end organ toxicity
• Toxicity is Reversible Grade 3/4 end organ toxicity - Not end organ destructive
Correlation – Limitations

DLT

Therefore, for the reported organ and tissue dosimetry for an MTD for a radiotherapeutic

• Minimal or no correlation to an actual end organ reversible toxicity for virtually all reported organs

• End organ toxicities are reversible (Grade 3/4) not organ destructive
Correlation – Limitations
DLT

The radiation exposures are not predictive for prospective therapeutic efficacy or organ safety for

- The studied radiotherapeutic in the target population
- are not generalizable to any other radiotherapeutic or any other target population
Dose-Dosimetry Correlation Model for Redesign of Therapeutic Dose Schedule

Retrospective Redesign

- Completed Initial/first in humans MTD
- Relate adverse events/dosimetry data retrospectively to correlate therapeutic dose to radiation dosimetry
- Postulate radiation dosimetry/patient specific dose model
- Dose/dosimetry model must be evaluated in Phase 1/2 safety/efficacy clinical trial
Dose-Dosimetry Correlation Model for Redesign of Therapeutic Dose Schedule

Dose/Dosimetry Models

• Whole Body Radiation Dose - Bexxar
• Organ specific radiation dose
  Liver, kidney, lung
• Tumor specific radiation dose ???
Dosimetry Utilization in Clinical Trial Safety Design

Whole Body Biodistribution Images & Organ/Tissue Dosimetry -> “Roadmap”

Utilized to design clinical trial safety assessment schema to monitor for adverse events
Dosimetry Utilization in Clinical Trial Safety Design

Roadmap elements

• “Imaged” & non-imaged organs

• Clearance pathways
  - Kidney - Urinary
  - Liver – Biliary tract – Bowel

• Tumor uptake
Dosimetry Utilization in Clinical Trial Safety Design

Roadmap focuses safety monitoring schema

- Clinical history & physical
- Laboratory
- Radiographic
Enrollment strategies

- 3 together – potential to exceed maximum of 2 DLTs in cohort

- 1 - observe without DLT 6 – 8 weeks
  - Enroll 2

- 2 - observe without DLT 6 – 8 weeks
  - Enroll 1
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Figure 5: Research Support for Product Development

Translational Research

Critical Path Initiative


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Thank you