Regulatory Challenges In the Use of Healthy Volunteers

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Healthy Volunteer Studies in Oncology Drug Development:
Pivotal Considerations Toward Optimal Deployment
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Outline

- Historical perspective on early phase trials
- Important aspects of HV studies
- FDA considerations for HV studies
- Immuno-oncology agents
  - Case example
  - Trial design challenges

Early phase clinical trials in oncology: historical perspective

- Patients with advanced stage or refractory cancers
- Primary objective is safety
  - Possibility that some cancer patients may benefit
- Primarily genotoxic drugs
  - Desire to protect healthy volunteers (HV) from exposure

Early phase clinical trials in oncology: historical perspective

- Regulatory guidance documents:
  - International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) S9 guideline (EU, Japan, USA)
  - ICH M3 guideline: HV
  - Committee for Medicinal Products for Human Use anticancer guidance (EMA)
  - FDA Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers

Healthy volunteers

- Availability of non-cytotoxic drugs permits conduct of studies in HV
- Advantages of HV studies include:
  - Investigation of bioavailability/pharmacokinetics
  - Data not confounded by disease state
  - Reduction in patient exposure to ineffective drugs or doses
  - Rapid subject accrual

Healthy volunteers

- Disadvantages of HV studies include:
  - Extrapolation of results to cancer patients may be limited
  - Low-dose pharmacokinetics in HV may be different from therapeutic dose pharmacokinetics in oncology patients
    - Sources of interpatient PK variability: abnormalities of absorption, distribution, elimination, and protein binding
  - Single dose does not allow for characterization at steady state

Healthy volunteer studies

- Primary objectives typically pharmacokinetic evaluation and metabolic profiling; pharmacodynamics evaluated as secondary objectives
- Other objectives: dose finding, formulation development, safety, diagnostic imaging

Drug interaction assessment: HV studies

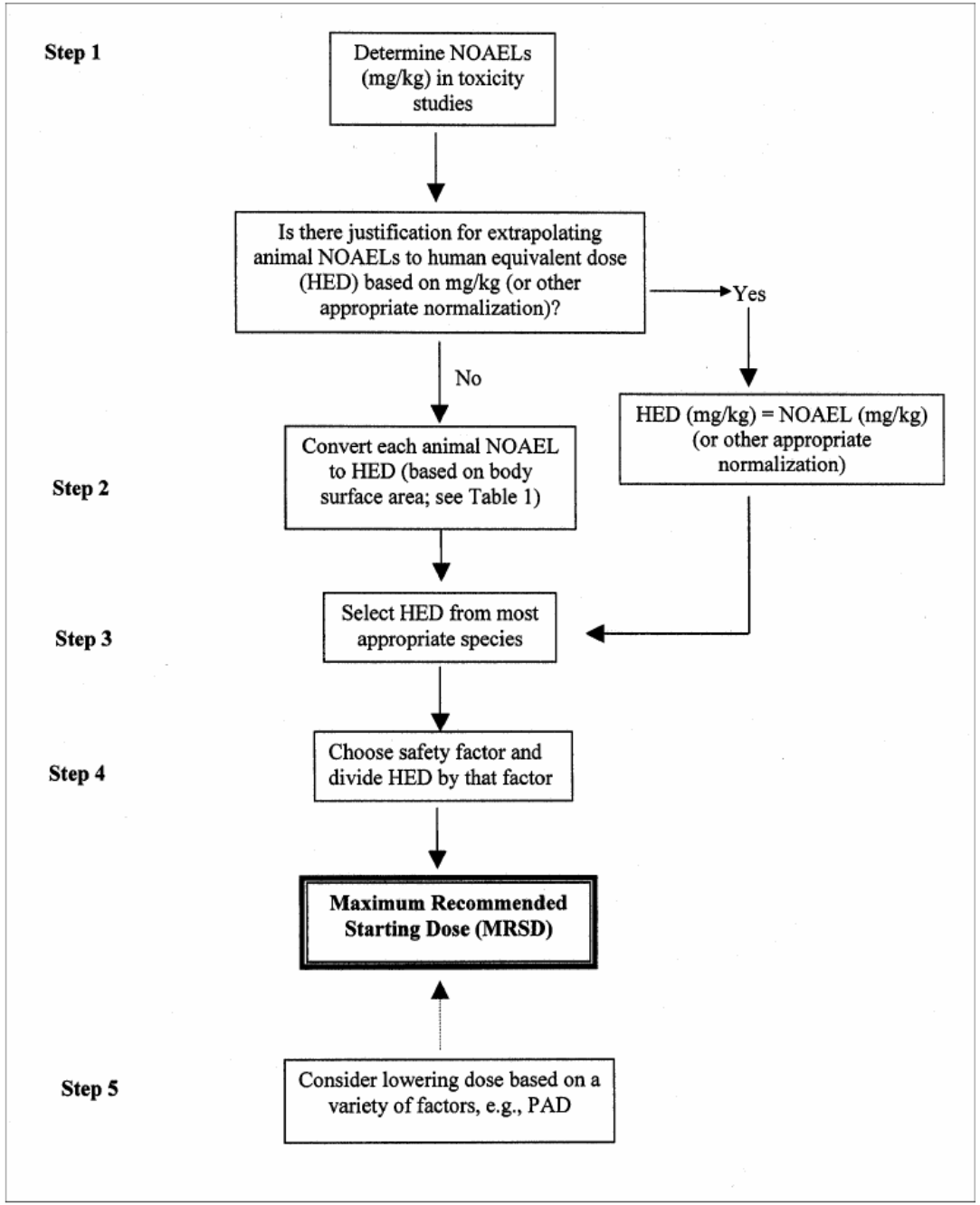
- Oncology drug CYP3A interaction assessments
  - Assessment of CYP inducer (rifampin) and inhibitor (itraconazole) on PK of experimental oncology drugs metabolized by CYP3A
- Co-administered agent-drug interaction studies before initiation of later phase trials to inform dosing
- Evaluation of changes in gastric pH when given with PPIs, H2 antagonists, or salt-based antacids

PK and PD assessments: HV studies

- Expanded numbers of HV at each dose level during escalation
  - Full characterization of PK profile
  - Minimization of subtherapeutic dose administration
- Collection of biomarkers from HV to guide starting dose and patient selection in early oncology patient studies
  - Example: Imprime PGG and ABA

FDA Guidance for Industry for HV studies

- Outlines an algorithm for deriving the maximum recommended starting dose (MRSD) for first-in-human clinical trials in adult HV
- Recommends a standard process by which the MRSD can be selected



https://www.fda.gov/downloads/drugs/guidances/ucm078932.pdf

FDA considerations for HV studies

- Genotoxic studies essential (at least *in vitro, in vivo* encouraged)
- The default safety factor is usually 10 due to variability in extrapolating from animal toxicity studies to studies in humans
  - Difficulty in detecting certain toxicities in animals (headache, myalgia)
  - Differences in receptor densities or affinities
  - Interspecies differences in ADME

Nambiar 2012

FDA considerations for HV studies

- Safety pharmacology studies in accordance with ICH M3, S7A, and S7B
- Effects on major organ systems
- Preclinical toxicology
- Early detection of AEs

Clinical considerations for HV studies

- Limited exposure to drug (1-2 doses)
- Conservative dosing scheme
- Safety stopping rules necessary
  - Identify acceptable toxicities
  - Identify unacceptable toxicities and procedures for addressing them within the protocol

Healthy volunteer studies

- FDA review of proposals for phase 1 trials of anti-cancer drugs to be conducted in HV under US INDs from 2003-4 (8 HV studies):
  - Studies included signaling agents (2), receptor modulators (3), growth factors (2), chemoprevention agents (1)
  - Genotoxicity battery results included full batteries that were negative (7) and where *in vitro* studies were negative (1)
  - Starting dose ≤ 1/10th the rodent NOAEL (3), based on clinical data (5)
  - Single dose (6), two doses (1), daily dosing x 5 (1)

Dagher et al, *JCO* 23, no 16_suppl, 2005

Immuno-oncology agents: case report

- TGN1412: CD28 superagonist
  - First-in-class superagonist monoclonal antibody specific for the T-cell co-stimulatory molecule CD28
  - CD28 engages with ligands CD80 and CD86 on professional antigen presenting cells to stimulate T-cell responses
  - TGN1412 mediates T-cell activation through CD28 rather than through the T-cell receptor (TCR)

Hunig, Nature Reviews, 2012

Immuno-oncology agents: case report

- Double-blind, randomized, placebo-controlled phase 1 study of TGN1412 (TeGenero) in UK
- March 13, 2006: 6 HVs received an IV infusion of TGN1412 over 3-6 minutes; 2 HVs received placebo (saline)
- 6 HVs developed life-threatening cytokine release syndrome within 90 minutes of infusion and were admitted to the ICU within 12-16 hours of dosing
  - Pulmonary infiltrates and lung injury, renal failure, DIC, severe depletion of lymphocytes and monocytes
  - Patients received cardiopulmonary support, dialysis, high dose methylprednisolone, and an anti-interleukin-2 receptor antagonist antibody
  - Prolonged cardiovascular shock and ARDS developed in 2 patients

Suntharalingam et al, NEJM, 2006

TGN1412 – rodents

- CD28 superagonists cause polyclonal T-cell activation in rats with response dominated by T_{reg} cells
- T_{em} cells were the source of IFNγ, TNF, and IL-2 that mediated CRS in HV
  - Accumulation of T_{em} cells is driven by exposure to infectious agents, not seen in laboratory rodents
  - T_{em}>T_{reg} cells in humans is disadvantageous when exposed to TGN1412

Hunig, Nature Reviews, 2012

TGN1412 – primates and PBMCs

- TGN1412 had been given to cynomolgus macaques at 500x the dose given to HV
  - Macaque CD4+ T cells lose CD28 expression during their differentiation into T_{em} cells
- TGN1412 does not elicit a cytokine or proliferative response when added to PBMC culture using a soluble format; however, it does elicit a response in PBMCs using a plate bound format or in some high density T-cell pre-cultures which allow for cross-linking of the receptor

Hunig, Nature Reviews, 2012

TGN1412: Lessons learned

- Potential failure of the NOAEL-based calculations of FIH doses
  - If animal model fails to respond, dose escalation can lead to high level from which the human starting dose is calculated
- Clinical trials of monoclonal antibodies: MABEL method

Hunig, Nature Reviews, 2012

Immuno-oncology agents

- Target the anti-tumor activity of a patient's immune system
- Monoclonal antibodies directed against immunomodulatory molecules expressed at the surface of immune and tumor cells
- New challenges in development of phase 1 trials

Immuno-oncology trial design challenges

- Dose-limiting toxicities and MTD definition
  - Late onset DLTs
  - RP2D based on MAD
- Variety of dosing schedules
- Large expansion cohorts
- Predictive biomarker studies
- Patient eligibility

Conclusions

- Evaluation of genotoxicity necessary
- Estimation of starting dose via FDA guidance or other supported method
- Limitation of clinical exposure
- Immuno-oncology agents may require new thinking about early trial design

Questions

- In which studies should healthy volunteers be considered to aid in oncologic drug development?