Regulatory Challenges In the Use of Healthy Volunteers

ASCPT Annual Meeting
Healthy Volunteer Studies in Oncology Drug Development:
Pivotal Considerations Toward Optimal Deployment
March 23, 2018

Nicole Drezner, MD
Medical Officer
Office of Hematology and Oncology Products
U.S. Food and Drug Administration
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
Step 1
Determine NOAELs (mg/kg) in toxicity studies

Is there justification for extrapolating animal NOAELs to human equivalent dose (HED) based on mg/kg (or other appropriate normalization)?

Yes

Step 2
Convert each animal NOAEL to HED (based on body surface area; see Table 1)

No

HED (mg/kg) = NOAEL (mg/kg)
(or other appropriate normalization)

Step 3
Select HED from most appropriate species

Step 4
Choose safety factor and divide HED by that factor

Maximum Recommended Starting Dose (MRSD)

Step 5
Consider lowering dose based on a variety of factors, e.g., PAD
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 \textit{in vitro} studies were negative (1)
  - Starting dose $\leq 1/10^{th}$ the rodent NOAEL (3), based on clinical data (5)
  - Single dose (6), two doses (1), daily dosing x 5 (1)

Dagher et al, \textit{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 $T_{\text{reg}}$ cells
- $T_{\text{em}}$ cells were the source of IFN$\gamma$, TNF, and IL-2 that mediated CRS in HV
  - Accumulation of $T_{\text{em}}$ cells is driven by exposure to infectious agents, not seen in laboratory rodents
  - $T_{\text{em}} > T_{\text{reg}}$ 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?