Regulatory Recommendations for Nonclinical Studies of Anticancer Pharmaceuticals

Todd Palmby, PhD
Pharmacology/Toxicology Supervisor
Office of Hematology and Oncology Products

Food and Drug Administration
10903 New Hampshire Avenue,
Silver Spring, Maryland 20993
White Oak Campus, Building 22, Room 1315

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What is the Issue?

- Cardiovascular toxicity of pharmaceuticals are not always predicted by in vitro and animal safety studies
  - If nonclinical studies do not inform appropriate monitoring in clinical trials, then mechanism, severity, incidence and long-term impact on the patient not characterized prior to regulatory approval
  - Mitigation or treatment strategies for cardiovascular toxicities often not explored during drug development
  - May not screen for potential of known cardiovascular toxicity in next generation products

Goals of this Session

- Discuss in vitro and in vivo nonclinical models to assess cardiovascular toxicity
  - Utility to identify the level of potential risk or elucidate mechanism
  - Cases when additional nonclinical cardiovascular safety studies may be warranted and timing of when they should be conducted (e.g., up front IND-enabling or after toxicity is observed in patients)

Regulatory Guidances for Nonclinical Cardiovascular Safety Studies

- ICH M3(R2)
  - Nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals
- ICH S6(R1)
  - Pre-clinical safety evaluation of biotechnology-derived pharmaceuticals
- ICH S9
  - Nonclinical evaluation for anticancer pharmaceuticals
- ICH S7(A) and ICH S7(B)
  - Safety pharmacology studies for human pharmaceuticals

ICH S9: Nonclinical Evaluation of Anticancer Pharmaceuticals

- Pharmaceuticals that are intended to treat cancer in patients with serious and life threatening malignancies
- Provide recommendations on type and timing of nonclinical studies in relation to the development of anticancer pharmaceuticals
- Includes both small molecule and biotechnology-derived pharmaceuticals (although S6 is generally referenced)
- “This guidance aims to facilitate and accelerate the development of anticancer pharmaceuticals and to protect patients from unnecessary adverse effects…”

ICH S9: Nonclinical Data to Assess Potential for Cardiovascular Toxicity

- In general, 28-day repeat-dose toxicity studies in 2 species (rodent and non-rodent) with similar route and schedule can support Phase 1 and 2 clinical trials with continuous dosing
  - Clinical chemistry (e.g., creatine kinase, aspartate transaminase, lactate dehydrogenase, troponin)
  - Organ weights (heart)
  - Histopathology (heart)
  - ECG in non-rodent
- hERG assay (not always included)

ICH S7A: Safety Pharmacology Studies

- Definition:
  - studies that investigate the potential undesirable pharmacodynamic effects of a substance on physiological functions in relation to exposure in the therapeutic range and above
- Objectives:
  - to identify undesirable pharmacodynamic properties of a substance that may have relevance to its human safety
  - to evaluate adverse pharmacodynamic and/or pathophysiological effects of a substance observed in toxicology and/or clinical studies
  - to investigate the mechanism of the adverse pharmacodynamic effects observed and/or suspected

ICH S7A and ICH S7B

- Detection of pro-arrhythmic risks much better as a result of additional testing and monitoring
  - Nonclinical: hERG assay, Purkinje fiber assays, intact heart, animal CV safety pharmacology studies (ICH-S7A and ICH-S7B Guidances)
  - Clinical: Human ECGs and thorough QT/QTc studies (ICH-E14 Guidance)
- Failure to prevent or anticipate cardiovascular risk in humans continues to occur, particularly with pharmaceuticals that do not specifically interfere with cardiac ion channels

ICH S9: Safety Pharmacology

- Safety pharmacology includes an assessment of the effect on cardiovascular system
  - Could be included in general toxicology studies
  - Detailed clinical observations following dosing and appropriate electrocardiographic measurements in nonrodents are generally considered sufficient
  - Conducting stand-alone safety pharmacology studies not warranted
  - In cases where specific concerns have been identified that could put patients at significant additional risks in clinical trials, appropriate safety pharmacology studies described in ICH S7A and/or S7B should be considered.

SOME DIFFERENCES BETWEEN ICH S9 AND ICH M3(R2) …

ICH S9 vs. ICH M3(R2): Studies and Timing

ICH S9		ICH M3(R2)	
Studies	**Timing**	**Studies**	**Timing**
Safety Pharmacology parameters can be incorporated into general toxicology studies	prior to Phase 1	Core battery of Safety Pharmacology studies (ICH S7A and S7B)	prior to Phase 1

ICH S9 vs. ICH M3(R2): Studies and Timing

General Toxicology – Clinical Development

ICH S9		ICH M3(R2)	
Studies	**Timing**	**Studies**	**Timing**
28 day repeat dose toxicity studies (rodent and non-rodent)	support single through continuous dosing (if patient benefits)	Repeat dose toxicity studies (rodent (r) and non-rodent (n)) similar to clinical trial duration (i.e., ≤ 2 week trial = 2 week studies; 2 week – 6 month trial = same duration for studies; > 6 month trial = 6 (r) and 9 (n)* month studies)	prior to conducting clinical trials

* 6 month studies in non-rodents may be acceptable (e.g., treatment of cancer recurrence, short life expectancy, etc.)

ICH S9 vs. ICH M3(R2): Studies and Timing

General Toxicology – Marketing

ICH S9		ICH M3(R2)	
Studies	**Timing**	**Studies**	**Timing**
3 month repeat dose toxicity studies (rodent (r) and non-rodent (n))	prior to Phase 3; marketing	Repeat dose toxicity studies (r and n) similar to treatment duration (i.e., ≤ 2 week treatment = 1 month studies; 2 week – 1 month treatment = 3 month studies; 1 – 3 month treatment = 6 month studies; > 3 month treatment = 6 (r) and 9 (n)* month studies)	supports marketing

* 6 month studies in non-rodents may be acceptable (e.g., treatment of cancer recurrence, short life expectancy, etc.)

Why has Cardiovascular Toxicity Persisted in Oncology Drug Development?

- Risk-Benefit evaluation
  - Patients and healthcare providers are willing to accept a certain level of toxicity and risk
  - Need for better pharmaceuticals to treat patients with various cancers
- Cardiovascular toxicity may not always be separated from anti-tumor activity
  - Not always traditional “off-target” effects
  - Cardiovascular toxicities may be related to the primary mechanism of action

Oncology Treatment is Changing

- Multiple therapies approved for some indications
  - Need for treatments with better activity and better safety profile
- Patients with certain diseases have improved outcomes and longer life expectancies (e.g., CML)
  - Long-term impact on cardiovascular system
- Evaluation of therapies in first- or second-line setting, patients with newly diagnosed (and potentially curable) disease, etc.

Room for Improvement? Focused Nonclinical Studies to Assess Cardiovascular Safety of Oncology Drugs

- Development of better models may improve screening of candidate drugs for potential cardiotoxicity and mechanistic characterization
- Are additional studies warranted based on findings in nonclinical or clinical studies?
- Is there potential to impact clinical development or use?
  - Better predict potential level of risk for cardiovascular toxicity
  - Identify appropriate clinical monitoring
  - Identify patients with relevant risk factors
  - Mitigate cardiovascular toxicity in patients


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