【S-6】

Elements of Carcinogenicity Study: Dose Selection and Justification

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A. INTRODUCTION:

In order to register a new drug application (NDA) as a new molecular entity or/and new chemical entity it usually requires to test carcinogenic potentials of the compound in addition to safety studies, primary and secondary pharmacology studies, pharmacokinetics, toxicokinetics, single- and repeated-toxicology, genotoxicity and reproductive toxicity studies. Carcinogenicity study is one of the most expensive ($5,000,000) and time consuming (2-3 years) preclinical studies. Therefore, industry and regulatory authorities from U.S., EU, and Japan formed International Conference of Harmonization (ICH) and agreements were issued with relevant observer entities.

The ICH produced guidance documents for carcinogenicity (CA) protocol submissions, which are attached at the end of this abstract for the future references. The guidance documents represent US regulatory agency's current thinking on the topic. But, it does not create or confer any rights for or on any person and does not operate to bind US FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

In general, CA study outcomes are needed before NDA registration. But, drugs for life-threatening or debilitating diseases without an alternative therapy may be preceded for post-approval. Oncolytic drugs for short life-expectancy may be used before CA studies. But, if life is prolonged by the drug, CA studies are need subsequently.

The main concerns for dose selection for CA studies are adequate margin of safety over human exposure and dose should be tolerable without significant dysfunction and be compatible with good survival. Thus, dose selection should be based on animal and human data so that meaningful extrapolations of animal data could be predictable for clinical relevancy. In rodent CA study, route of drug administration should be the same intended clinical route. Topical drugs generally need CA test such as photo carcinogenic potential

due to dermal application. If the topical agent is not absorbed dermally, no need to be tested after an oral administration. New formulated drug needs pharmacokinetic and toxicokinetic studies before contemplating CA studies. Endogenous recombinant human insulins, growth hormones, calcitonin and their analogues are generally exempt unless they are significantly different from the original hormones in chemical structure, biological effect, and pharmacokinetic profiles.

B. METHODS OF CARCINOGENICITY DOSE SELECTION:

Thus, the key endpoints of dose selection for CA studies are 1) toxicity based endpoints, 2) pharmacokinetic endpoints, 3) saturation of absorption, 4) pharmacodynamic endpoints, 5) maximum feasible dose, and 6) limit dose. Toxicity based endpoints are usually the maximum tolerated dose (MTD). The MTD is predicted to produce a minimum toxic effect over the course of CA study, which is generally chosen based on data derived from toxicity studies of 3-month duration (as we have harmonization among three regulatory parties).

1. Maximum Tolerated Dose.

If mean body weight or body weight gain decrement is criterion for the MTD, document the reduced food consumption is not a palatability problem. In this case, no more than 10% decrease in body weight gain relative to control animal groups is necessary without significant alterations in animal's normal life span or interfering with study interpretation. Mortality, clinical signs, organ weight, hematologic and clinical chemistry data and multiples of clinical exposure should be taken into consideration for the MTD selection and for its justification. Cardiac, liver or other target organ toxicities should be monitored in line with organ weight changes, clinical chemistry or microscopic histopathologic changes.

2. Pharmacokinetic Endpoint

Exposures at a high multiple of the human AUC (usually at the maximum recommended daily dose) may be an appropriate endpoint for dose selection for non-genotoxic pharmaceuticals. If pharmacokinetic or toxicokinetic endpoint is considered to be used for the top dose selection, pharmacokinetic data with AUC ratio for both parent and its human metabolites should be documented. The exposure ratio (25-fold) should be considered

sufficiently great to provide reassurance of an adequate test of CA study. In this case, metabolic profiles of animals and human should be comparable. Plasma protein binding data of parent and its major human metabolites and in animals should be also comparable. Likewisely, genotoxic potential of the parent and its major human metabolites in animals and human should be documented. Positive genotoxic compounds are excluded AUC ratio (25-fold) PK endpoint method and limit dose approaches.

3. Saturation of Absorption

The high dose selection is based on saturation of absorption measured by systemic availability of drug or substances such as active metabolites, which is acceptable. If the bioavailability as a function of drug doses reaches plateau and saturable in Cmax or AUC values, there is no need to test higher doses than the maximum saturation dose unless drug formulation is considered to be changed. The mid and low doses should take into account the relative exposures based on saturation and elimination phenomena.

4. Pharmacodynamic Endpoints

When choosing pharmacodynamic (PD) endpoints for a CA study, the high dose should produce a PD response such that additional dose escalation would be precluded. However, the dose should not disturb physiology or homeostasis that compromises the validity of study. Examples would be hypotension of antihypertensive drugs, hypoglycemia of anti-diabetic drugs, or inhibition of blood clotting.

5. Maximum Feasible Dose

Currently, the maximum feasible dose in feeding studies is considered 5% of the diet. When dosing is not from dietary administration, the high dose will be limited based on considerations including practicality and local tolerance such as solubility of the pharmaceuticals or volume to be administered.

6. Limit Dose

In cases where there is no toxicity including genetic toxicities and the maximum human dose does not exceed 500 mg per day, it may not be necessary to exceed as a dose of 1500 mg/kg/day in a rodent CA study. If the human dose exceeds 500 mg per day, the rodent dose may be increased to the maximum feasible dose. The rodent exposure at 1500

mg/kg/day should be 10-fold higher than the exposure at the maximum intended human dose.

Factors that one can consider for the selection of mid and low dose are: linearity of pharmacokinetics and saturation of metabolic pathways, human exposure and dose, pharmacodynamic response in rodents, alterations in normal rodent physiology, mechanistic information and the potential unpredictability of toxicities observed in short-term studies.

C. CONCLUSION:

It is not simple matter to select the acceptable dose for 2-year carcinogenicity study in rodents to predict potential human relevancy. The 6 methods that were outlined above are useful guidelines to pick the right dose. However, one has to analyze carefully the 13-week toxicology study for CA study dose selection and interpretation of the data.

D. ICH DOCUMENTS AS REFERENCES:

a) The need for long-term rodent CA studies (S1A)
b) Testing for CA pharmaceuticals (S1B)
c) Dose selection for CA studies of pharmaceuticals (S1C)
d) Addendum to dose selection for CA studies of pharmaceuticals: Addition of a limit dose {S1C(R)}
e) Guidance on specific aspects for genotoxicity test (S2A)
f) Genotoxicity: standard battery for genotoxicity test (S2B)
g) Toxicokinetics: assessment of systemic exposure (S3A)
h) Guidance for repeated dose tissue distribution (S3B)

Carcinogenity Study Guidance

Guidance for Industry

Dose Selection for Carcinogenicity Studies of Pharmaceuticals and its addendum (S1C)

Guidance for Industry. Addition of a Limit Dose and Related Notes [S1C(R)]

Dietary Restrictional Animal Model

- In cross species and strains of animal dietary restriction produces low body weight with extended life spam
- Total life spam of rats is usually 2 years which can be extended to 3 years that may be comparable to the life spam of human
- New evaluation and guide are needed

The Need for Long-Term rodent CA Study(S1A)

Continuous use for ≥ 6 months

Anesthetics, imaging agents, etc

Carcinogenic drug class

CA potential based on SAR

Preneoplastic lesions

Exempt of genotoxic drugs

Guidelines of ICH Documents

- Testing for CA of Pharmaceuticals(S1B)
- Dose Selection & Addendum(S1C)
- Limit Dose and Related Notes (S1C/R)
- CA Study Protocol Submissions
- Special Protocol (SX) Assessment
- Statistics, Design, Analysis, Interpretation
- CA Models Transgenic, Knockout models

Introduction.

Traditionally, carcinogenicity studies for chemical agents have relied upon the maximally tolerated dose (MTD) as the standard method for high dose selection The MTD is generally chosen based on data derived from toxicity studies of three months' duration

However, the above was not necessarily true in Europe and Japan

Now, we have harmonization among all three regulatory parties

Carcinogenicity Assessment Committee(CAC)

- Communication with sponsors
- Good order of documents, design, data, etc
- Dose selection and justification
- SX protocol for mouse & rat
- Review and report to CAC
- CAC meeting with members & statisticians
- CAC action and petitions for full CAC

Endpoints for Carcinogenicity Studies

- Toxicity based endpoints
- Pharmacokinetic endpoints
- Saturation of absorption
- Pharmacodynamic endpoints
- Maximum feasible dose
- Limit dose

Carcinogenicity Studies Toxicity Based Endpoints

The top dose, or MTD is that predicted to produce a minimum toxic effect over the course of the study

It is assumed that such an effect may be predicted from a 90-day dose range-finding study in which minimal toxicity is observed

Carcinogenicity Studies Toxicity Based Endpoints, Cont.

- No more than 10% decrease in body weight gain relative to controls (antiobesity drug?)
- Target organ toxicity
- Significant alterations in clinical pathological parameters

Carcinogenicity Studies Pharmacokinetic Endpoints

Exposures at a high multiple of the human AUC (usually at the maximum recommended daily dose) may be an appropriate endpoint for dose selection for a non-genotoxic pharmaceutic

The metabolic profiles should be similar in rodents and humans

The exposure ratio (25-fold) should be considered sufficiently great to provide reassurance of an adequate test of carcinogenicity

Carcinogenicity Studies Pharmacokinetic Endpoints, Cont.

Systemic comparisons of exposure is better assessed by blood concentrations of parent and metabolites than by nominal dose (but this is not always the case)

Some feel that the unbound drug in plasma is thought to be the most relevant indirect measure of tissue concentration of unbound drug

The AUC is considered the most comprehensive pharmacokinetic endpoint

Criteria for Comparisons of AUC in Animals and Man

- Use the same strains for all studies
- PK and TK studies should be of sufficient duration
- Metabolism should be similar between animals and man
- Judgement should be used whether exposure should be based on parent, metabolite, or both
- Protein binding should be taken into consideration
- Human estimates should be based on the maximum daily dose of pharmaceutic

Carcinogenicity Studies Saturation of absorption

High dose selection based on saturation of absorption measured by systemic availability of drug related substances is acceptable

The mid and low doses should take into account the relative exposures based on saturation and elimination phenomena.

Carcinogenicity Studies Pharmacodynamic Endpoints

When choosing a pharmacodynamic endpoint for a carcinogenicity study, the high dose should produce a pharmacodynamic response such that additional dose escalation would be precluded

Examples include hypotension, hypoglycemia, or inhibition of blood clotting, etc

Carcinogenicity Studies Maximum Feasible Dose

Currently, the maximum feasible dose in feeding studies is considered 5% of the diet

When dosing is not from dietary administration, the high dose will be limited based on considerations including practicality and local tolerance (solubility of the pharmaceutic, volume to be administered, etc)

Carcinogenicity Studies Limit Dose

In cases where there is no toxicity (including genetic toxicity), and the maximum human dose does not exceed 500 mg/day, it may not be necessary to exceed a dose of 1500 mg/kg/day in a rodent carcinogenicity study

If the human dose exceeds 500 mg/day, the rodent dose may be increased to the maximum feasible dose

The rodent exposure at 1500 mg/kg/day should be 10-fold higher than the exposure at the maximum intended human dose

Selection of Mid & Low Dose

Factors for Consideration

- Linearity of pharmacokinetics and saturation of metabolic pathways
- Human exposure and dose
- Pharmacodynamic response in rodents
- Alterations in normal rodent physiology
- Mechanistic information
- The unpredictability of toxicities observed in short-term studies (used to set the high dose for the two year study)