Dose Selection for Carcinogenicity Studies of Pharmaceuticals
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Dose selection for carcinogenicity studies is a controversial topic, which has been much discussed in the ICH so far. Through the discussion, we are encouraged to re-consider the traditional high dose selection methods, such as those based on maximally tolerated dose (MTD), toxicity endpoint, or multiples of recommended clinical daily dose. Ideally, the doses selected for carcinogenicity studies should provide exposures that: (1) allow an adequate margin of safety over the human therapeutic exposure, (2) are tolerated without significant chronic physiological dysfunction and are compatible with good survival, (3) are guided by a comprehensive set of animal and human data that focuses broadly on the properties of the agent and the suitability of the animal, and (4) permit data interpretation in the context of clinical use.

Dose selection usually requires to consider various endpoints, and the endpoints are determined based on the results of preliminary dose-ranging studies. The mutually acceptable criteria achieved in the ICH are as follows.

1) Carcinogenicity studies are carried out in a limited number of rat and mouse strains for which there are reasonable information on spontaneous tumor incidence. Ideally, rodent species/strains with metabolic profiles as similar as possible to humans should be studied.

2) Dose-ranging studies should be conducted for both males and females.

3) Dose selection is generally determined from 90-day studies using the route and method of administration that will be used in the carcinogenicity study.

4) Selection of an appropriate dosing schedule and regimen should be based on clinical use and exposure patterns, pharmacokinetics, and practical considerations.

5) Consideration should be given to toxic signs and dose-response relationship, and to the carcinogenic changes observed in the general toxicity studies, such as the occurrence of preneoplastic lesions and/or tissue-specific proliferative effects, and disturbances in endocrine homeostasis.

6) Changes in metabolite profile or alterations in metabolizing enzyme activities (induction or inhibition) over time should be considered.
The ICH Expert Working Group on Safety provided the following five endpoints for the high dose selection.

1) Pharmacodynamic endpoints
   Pharmacodynamic endpoints for high dose selection will be highly compound-specific and are considered for individual study designs on the basis of scientific rationale. The high dose selected should not produce disturbances of physiology or homeostasis.

2) Toxicity-based endpoints
   Toxicity-based endpoints for high dose selection is based on the pharmacological properties and toxicological profile of the test compound, and is toxicologically equivalent to MTD.

3) Pharmacokinetic endpoints
   The AUC is considered the most comprehensive pharmacokinetic endpoint since it takes into account the plasma concentration of the compound and residence time in vivo. The following criteria for comparisons of AUC in animals and human are especially applicable for use of a pharmacokinetically-defined exposure for high dose selection.
   ① Rodent pharmacokinetic data are derived from the strains used for the carcinogenicity studies using the route of compound administration and dose ranges planned for the carcinogenicity study.
   ② Pharmacokinetic data are derived from studies of sufficient duration to take into account potential time-dependent changes in pharmacokinetic parameters.
   ③ Documentation is provided on the similarity of exposure to parent compound and metabolites between rodents and humans.
   ④ In assessing exposure, scientific judgment is used to determine whether the AUC comparison is based on data for the parent, parent and metabolite(s) or metabolite(s). The justification for this decision is provided.
   ⑤ Interspecies differences in protein binding are taken into consideration when estimating relative exposure.
   ⑥ Human pharmacokinetic data are derived from studies encompassing the maximum recommended human daily dose.

In order to select a multiple of the human AUC that would serve as an acceptable endpoint for dose selection for carcinogenicity studies, a retrospective analysis was performed on the FDA database of carcinogenicity studies conducted at the MTD for which there was
sufficient human and rodent pharmacokinetic data for comparison of AUC values. As a result, a minimum systemic exposure ratio of 25 to attain an AUC value 25-fold greater than that of compound/metabolite in human plasma is proposed as an acceptable pharmacokinetic endpoint for high dose selection in case of an extremely low toxic compound.

4) 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 selected for the carcinogenicity study should take into account saturation of metabolic and elimination pathways.

5) Maximum feasible dose

For selecting middle and low doses, the following points should be considered:
1. Linearity of pharmacokinetics and saturation of metabolic pathways
2. Human exposure and therapeutic dose
3. Pharmacodynamic response in rodents
4. Alterations in normal rodent physiology
5. Mechanistic information and potential for threshold effects
6. The unpredictability of the progression of toxicity observed in short term studies.

The following practical cases were introduced and discussed concerning the variety and difficulties of dose selection for carcinogenicity studies: (1) MTD with AUC saturation, (2) comparison between feed admix and forced administration, (3) MTD on the extension of pharmacological effect, (4) Extremely low toxicity, (5) MTD without the correlation of pharmacokinetic profile, and (6) MTD and toxic mechanism.