Dose Selection for Carcinogenicity Studies of Pharmaceuticals

Introduction

Traditionally, carcinogenicity studies for chemical agents have relied upon the maximally tolerated dose (MTD) as the standard method for high dose selection (NOTE 1). The MTD is generally chosen based on data derived from toxicity studies of 3 months' duration.

In the past, the criteria for high dose selection for carcinogenicity studies of human pharmaceuticals have not been uniform among international regulatory agencies. In Europe and Japan, dose selection based on toxicity endpoints or attaining high multiples of the maximum recommended human daily dose (>IOOX on a milligram per kilogram (mg/kg) basis) have been accepted. However, in the United States, dose selection based on the MTD has traditionally been the only acceptable practice. All regions have used a maximum feasible dose as an acceptable endpoint.

For pharmaceuticals with low rodent toxicity, use of the MTD may result in the administration of very large doses in carcinogenicity studies, often representing high multiples of the clinical dose. The usefulness of an approach developed for genotoxic substances or radiation exposure where a threshold carcinogenic dose is not necessarily definable may not be appropriate for nongenotoxic agents (NOTE 2). For nongenotoxic substances where thresholds may exist and carcinogenicity may result from alterations in normal physiology, linear extrapolations from high dose effects have been questioned. This has led to the concern that exposures in rodents greatly in excess of the intended human exposures may not be relevant to human risk, because they so greatly alter the physiology of the test species, the findings may not reflect what would occur following human exposure.

Ideally, the doses selected for rodent bioassays for nongenotoxic pharmaceuticals should provide an exposure to the agent that (1) allows an adequate margin of safety over the human therapeutic exposure, (2) is tolerated without significant chronic physiological dysfunction and are compatible with good survival, (3) is guided by a comprehensive set of animal and human data that focus broadly on the properties of the agent and the suitability of the animal, and (4) permits data interpretation in the context of clinical use.

In order to achieve international harmonization of requirements for high dose selection for carcinogenicity studies of pharmaceuticals, and to establish a rational basis for high dose selection, the ICH Expert Working Group on Safety initiated a process to arrive at mutually acceptable and scientifically based criteria for high dose selection. Several features of pharmaceutical agents distinguish them from other environmental chemicals and can justify a guideline which may differ in some respects from other guidelines. This should enhance the relevance of the carcinogenicity study for pharmaceuticals. Thus, much knowledge may be available on the pharmacology, pharmacokinetics, and metabolic disposition

in humans. In addition, there will usually be information on the patient population, the expected use pattern, the range of exposure, and the toxicity and/or side effects that cannot be tolerated in humans. Diversity of the chemical and pharmacological nature of the substances developed as pharmaceuticals, plus the diversity of nongenotoxic mechanisms of carcinogenesis calls for a flexible approach to dose selection. This document proposes that any one of several approaches may be appropriate and acceptable for dose selection, and should provide for a more rational approach to dose selection for carcinogenicity studies for pharmaceuticals. These include: (1) Toxicitybased endpoints; (2) pharmacokinetic endpoints; (3) saturation of absorption; (4) pharmacodynamic endpoints; (5) maximum feasible dose; (6) additional endpoints

Consideration of all relevant animal data and integration with available human data is paramount in determining the most appropriate endpoint for selecting the high dose for the carcinogenicity study. Relevant pharmacokinetic, pharmacodynamic, and toxicity data should always be considered in the selection of doses for the carcinogenicity study, regardless of the primary endpoint used for high dose selection.

In the process of defining such a flexible approach, it is recognized that the fundamental mechanisms of carcinogenesis are only poorly understood at the present time. Further, it is also recognized that the use of the rodent to predict human carcinogenic risk has inherent limitations, although this approach is the best available option at this time. Thus, while the use of plasma levels of drug-derived substances represents an important attempt at improving the design of the rodent bioassay, progress in this field will necessitate continuing examination of the best method to detect human risk. This guideline is therefore intended to serve as guidance in this difficult and complex area recognizing the importance of updating the specific provisions outlined below as new data become available.

General Considerations for the Conduct of Dose-Ranging Studies

The considerations involved when undertaking dose-ranging studies to select the high dose for carcinogenicity studies are the same regardless of the final endpoint utilized.

1. In practice, 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 (NOTE 3).

2. Dose-ranging studies should be conducted for both males and females for all strains and species to be tested in the carcinogenicity bioassay.

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

4. Selection of an appropriate dosing schedule and regimen should be based on clinical use and exposure patterns, pharmacokinetics, and practical considerations. 5. Ideally, both the toxicity profile and any dose-limiting toxicity should be characterized. Consideration should also be given to general toxicity, 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 understood to allow for appropriate interpretation of studies.

Toxicity Endpoints in High Dose Selection

ICH 1 agreed to evaluate endpoints other than the MTD for the selection of the high dose in carcinogenicity studies. These were to be based on the pharmacological properties and toxicological profile of the test compound. There is no scientific consensus of the use of toxicity endpoints other than the MTD. Therefore, the ICH Expert Working Group on Safety has agreed to continue use of the MTD as an acceptable toxicity-based endpoint for high dose selection for carcinogenicity studies.

The following definition of the MTD is considered consistent with those published previously by international regulatory authorities (NOTE 1): The top dose or maximum tolerated dose is that which is predicted to produce a minimum toxic effect over the course of the carcinogenicity study. Such an effect may be predicted from a 90 day dose range-finding study in which minimal toxicity is observed. Factors to consider are alterations in physiological function which would be predicted to alter the animal's normal life span or interfere with interpretation of the study. Such factors include: No more than 10 percent decrease in body weight gain relative to controls; target organ toxicity; significant alterations in clinical pathological parameters.

Pharmacokinetic Endpoints in High Dose Selection

A systemic exposure representing a large multiple of the human AUC (at the maximum recommended daily dose) may be an appropriate endpoint for dose selection for carcinogenicity studies for nongenotoxic pharmaceuticals (NOTE 2) which have similar metabolic profiles in humans and rodents and low organ toxicity in rodents (high doses are well tolerated in rodents). The level of animal systemic exposure should be sufficiently great, compared to exposure to provide reassurance of an adequate test of carcinogenicity.

It is recognized that the doses administered to different species may not correspond to tissue concentrations because of different metabolic and excretory patterns. Comparability of systemic exposure is better assessed by blood concentrations of parent drug and metabolites than by administered dose. The unbound drug in plasma is thought to be the most relevant indirect measure of tissue concentrations of unbound drug. 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.

There is as yet, no validated scientific basis for use of comparative drug plasma