Points to consider on the non-clinical safety evaluation of anticancer drugs

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ABSTRACT — Since malignant tumors are life-threatening, the death rate from these diseases is high, and existing therapies have limited effectiveness, it is desired to provide new effective anticancer drugs to tumor patients sooner. However, there is no guideline regarding non-clinical safety studies on the development of anticancer drugs required for the first in human clinical trials and for the approval applications in Japan. Then, the Ministry of Health, Labour and Welfare (MHLW) established the collaboration group including regulatory, academic and industrial scientists to prepare the guideline on the non-clinical safety evaluation of anticancer drugs in 2004. As a guide for basic concept of non-clinical safety studies on anticancer drugs, the “Points to Consider” document was prepared by this group in 2007.

Key words: Points to consider, Non-clinical safety evaluation, Anticancer drugs,
First in human clinical trial, Approval application

INTRODUCTION

For the test methods of non-clinical safety studies required for applications for approval to manufacture (import) drugs, various guidelines for test methods including “Guidelines for Toxicity Studies of Drugs” (Guideline for Toxicity Studies; MHW, 1989) have been published, and for the timing of non-clinical studies, “Non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals” (M3 Guideline; MHW, 1998) specifies the timing. A wide variety of anticancer drugs have been developed, including those that directly or indirectly act on the cells causing cell death, primarily having what is called cytotoxicity, those that selectively block molecules involved in the signaling for cell growth in the new blood vessels required for proliferation of malignancy, and those that are highly selective because of their molecular structure such as tumor-specific antibodies. Since the existing non-clinical safety studies may not adequately examine high dose exposure over the clinical dosage range, or because of animal species specificity to the target molecules (i.e., some animal species do not respond to achieve the goal of the studies), or because of the severity of indicated disease, the therapeutic dosage and observed adverse reaction dose level may be close to each other, and for the social responsibility for providing patients with effective agents sooner, the type and duration of non-clinical safety studies are currently conducted on a case-by-case basis. However, because there is no basic concept, and because of these agents’ clinical particularity that they are administered to patients from Phase I clinical trials, the study items and study contents may be inappropriate due to the varied concept of anticancer drugs, or the timing of study conduct may be inappropriate, and thus...
studies are not always conducted appropriately. Then, aiming for more appropriate safety evaluations are conducted at the appropriate time, as a guide for basic concept of non-clinical safety studies on anticancer drugs, “Points to consider on non-clinical safety evaluation of anticancer drugs” (Points to Consider) was established. With respect to cytotoxic anticancer drugs, “Q&A for toxicity studies conducted for clinical trials and approval applications for anticancer agents” (MHLW, 2004) was also published.

The objective of this “Points to Consider” is to minimize the risk of patients, and to promote the development of anticancer drugs by presenting the basic concept of non-clinical safety studies required prior to the initiation of Phase I clinical trials and approval applications for anticancer drugs in Japan.

However, it is basically difficult to specify a uniformed concept for all anticancer drugs. In addition, as the developmental stage of drugs advances, resulting in a great number of findings, conduct of new additional studies may be required. Therefore, so long as the results are beneficial to the clinical safety evaluation, the concept presented here is not always to be observed.

This “Points to Consider” should be applied to non-clinical safety evaluation of anticancer drugs developed for the purpose of providing cancer patients with some clinical benefits such as inhibition of progression and metastases of malignant tumor lesions, prolonged life and symptom relief. In the case of biologic anticancer drugs that have species-specific biological reactivity, the guideline entitled “Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals” (MHW, 2000) should also be taken into consideration when planning the appropriate safety evaluation studies.

Questions and answers for this “Points to Consider” are available in Supplemental Data.

**BASIC CONCEPT OF NON-CLINICAL SAFETY STUDIES**

**General principles**

The objectives of non-clinical safety evaluations are to 1) establishment of a safe initial dose level for the first human exposure, 2) clarification of the toxicological profile of a drug, e.g., identification of the target organs, estimation of the safety margin, and reversibility and 3) determining the proper endpoints to include for clinical adverse reaction monitoring. These objectives should be satisfied from the safety studies conducted in accordance with the “Guidelines for Toxicity Studies” (MHW, 1989) and “M3 Guideline” (MHW, 1998). However, because of the particularity of development of anticancer drugs, most often that Phase I clinical trials involve cancer patients; because the disease condition is progressive and fatal; because the treatment dose levels are often close to the adverse effect dose levels; because of the severity of disease; and because more effective new drugs are desired to be supplied to the patients sooner, the type and timing of safety studies of anticancer drugs may be different from those for other pharmaceuticals. This “Points to Consider” specifies the basic concept of the type and timing of safety studies in relation to the development of anticancer drugs, but it is difficult to specify a uniform concept because of the varied mechanism of actions for these drugs and the wide variety of indicated patient populations. Therefore, instead of adhering to this “Points to Consider”, based on the previously notified “Guidelines for Toxicity Studies” (MHW, 1989), “Guidance on Genotoxicity Tests of Pharmaceuticals” (MHW, 1999), “Guidance on Carcinogenicity Tests of Pharmaceuticals” (MHW, 1999), “Safety Pharmacology Studies for Human Pharmaceuticals” (S7 Guideline; MHW, 2001), “Immunotoxicity Studies for Human Pharmaceuticals” (MHLW, 2006) and “M3 Guideline” (MHW, 1998), and, at the same time, in light of the particular situations in which each anticancer drug in development is to be used, individually deciding the type and timing of safety studies from the scientific standpoint, the non-clinical safety should be appropriately evaluated.

Although this “Points to Consider” does not mention toxicokinetics, toxicokinetic assessments should be in compliance with “Note for Guidance on Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies” (MHW, 1996).

**Non-clinical safety studies involving cancer patients, required prior to the initiation of Phase I clinical trials**

1. **Single dose toxicity studies**

Single-dose toxicity studies should be conducted in two mammalian species as a rule (Notes 1 and 2). In at least one animal species, female and male animals should be studied, and approximate lethal dose should also be examined. The route of administration should be the clinical route of administration in humans as a rule. However, if the clinical route of administration in humans cannot deliver adequate exposure, the route of administration that can give a higher exposure level may be chosen.

2. **Repeated dose toxicity studies**

The schedule of administration (repeated administration or intermittent administration, intervals for intermit-
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tent administration) for the repeated dose toxicity studies should be chosen from the
standpoints of the pharmacological mechanism of action, the pharmacokinetics of the
drug, the reversibility of toxic findings and the administration schedule and route in clinical trials under consider-
ation.

The duration of administration should not always be
in compliance with “M3 Guideline” (MHW, 1998). Since
the primary objective of Phase I clinical trials is to deter-
mine a maximum tolerated dose (MTD) and dose limiting
toxicity (DLT), if non-clinical repeated dose toxicity stud-
ies clearly demonstrated the presence or absence of toxic-
ity by repeated dose administration. DLT and its mark-
er, based on the results of toxicity studies conducted with
shorter duration or a smaller number of cycles of admin-
istration, a clinical trial could be initiated. In the clinical
trials, the duration or number of cycles of administration
may be continuously increased according to the patient’s
response, and in this case, a new toxicity study would be
unnecessary.

Repeated dose toxicity studies should be conducted in
females and males of two animal species, a rodent and
non-rodent. Determination of no observed adverse effect
level (NOAEL) is not essential, but it is desirable to set
the dose level, so that an adverse reaction marker and
DLT could be determined. The accumulation and delayed
toxicity should also be considered.

3. Genotoxicity studies
As a rule, genotoxicity studies are not mandatory.

4. Reproductive and developmental toxicity studies
As a rule, reproductive and developmental toxicity
studies are not mandatory. However, the exclusion cri-
tera should include pregnant female patients, nursing
mother patients, and female patients who are possibly
pregnant. If the repeated dose toxicity studies suggested
the effect on male reproductive organs, male patients
should be instructed to practice strict contraception. Even
when reproductive and developmental toxicity studies are
not conducted, female patients of childbearing potential
may be included in a clinical trial if strict contraception is
observed (Note 3).

5. Local tolerance studies
When the clinical route of administration is parenteral,
a conduct of local tolerance studies should be consid-
ered. However, a detailed examination such as a histopatho-
logical examination on the administration site in single dose
or repeated dose toxicity studies can substitute local toler-
ance studies.

6. Safety pharmacology studies
Comply with the “S7 Guideline” (MHW, 2001).

Non-clinical safety studies required prior to the
initiation of Phase I clinical trials conducted in
healthy adults
Comply with the “M3 Guideline” (MHW, 1998).

Non-clinical safety studies required prior to the
approval application

1. Repeated dose toxicity studies
Repeated dose toxicity studies should be conducted in
males and females of two animal species, rodent and non-
rodent. However, when an anticancer drug applicable to
only male or female patients demonstrated no apparent
sex difference in short-term repeated dose toxicity studies
conducted in two animal species, and the pharmacokinetics
suggested no sex difference, long-term repeated dose
toxicity studies may be conducted in the sex that is sub-
ject to treatment in clinical practice. The administration
(daily administration or intermittent administration, inter-
vals for intermittent administration) for the repeated dose
toxicity studies should be chosen, taking the pharma-
ological, pharmacokinetic characteristics of the drug, the
reversibility of toxic findings, and administration in clini-
cal trials into consideration. The duration of administra-
tion should not be more than 6 months in rodents and 9
months in non-rodents as a rule, but considering the toxici-
ological characteristics of the anticancer drug and dura-
tion of treatment in clinical practice, setting a more appro-
priate duration may be desirable. The studies should be
designed so as to either one of the studies can examine
the reversibility.

2. Genotoxicity studies
As a rule, genotoxicity studies should be required. How-
ever, when genotoxicity is predicted from the mecha-
anism of action and so on, the standard battery of genoto-
xicity studies may be partially omitted.

3. Carcinogenicity studies
Normally, carcinogenicity studies are not required.
See “Guidance on genotoxicity tests of pharmaceuticals”
(MHW, 1999) for details.

4. Reproductive and developmental toxicity studies
As a rule, reproductive and developmental toxicity
studies are required. However, if the mechanism of action has been suggested to have an embryonic lethality or teratogenicity, the reproductive and developmental toxicity studies may not be required for an approval application. In these cases, pregnant female patients, nursing mother patients, and female patients who are possibly pregnant are contraindicated, and female patients of childbearing potential and male patients are instructed to practice strict contraception.

When the reproductive and developmental toxicity, especially teratogenicity is to be examined, because of the nature of the drug such as potent maternal toxicity or embryonic lethality, the duration of administration or intervals varied from those specified in “Guidelines for Toxicity Studies” (MHW, 1989) must be considered. In this case, the rational for it requires scientific explanations.

5. Immunotoxicity studies
Comply with the “Immunotoxicity Studies for Human Pharmaceuticals” (MHLW, 2006).

6. Safety pharmacology studies
As a rule, safety pharmacological studies are required. See “S7 Guideline” (MHW, 2001) for details.

Notes
Note 1: In setting the initial dose for the Phase I clinical trials, if there is a scientific rationale for administration to rodents, a study in non-rodents is not always required.

Note 2: “Guideline for Clinical Evaluation of Anti-Malignant Tumor Agents” (MHLW, 2005) specifies that the initial dose of Phase I clinical trials should be 1/10 of the 10% lethal dose (LD_{10}) in mice presented by mg/m² as a rule, and if this dose demonstrated toxicity in other animal species, based on the animal species showing maximum sensitivity, the initial dose should be lower than a minimum dose showing no irreversibility. From these above, when a drug is to be administered to humans for the first time in Japan, studies should be designed so as to establish a toxic dose such as LD_{10} in mice, which is to be a rationale for deciding the initial dose. However, when reliable foreign Phase I clinical trial results or treatment results in humans are available, the initial dose for Phase I clinical trials can be chosen from those other than the results of non-clinical safety studies.

Note 3: Female patients of childbearing potential should be confirmed the possibility of pregnancy, and male patients and female patients of childbearing potential should be instructed to practice contraception for an appropriate period after the end of treatment period.

Supplemental Data:
Supplemental data are available at the on-line version of this article (http://www.joxsci.org).

REFERENCES