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Non-neoplastic lesions found only in the two-year bioassays but not in shorter toxicity studies of rats

Mizuho Nonaka [a], Kouhei Amakasu [a], Yukie Saegusa [a], Misaki Naota [a], Takuya Nishimura [a], Kumiko Ogawa [b], Akiyoshi Nishikawa [b, *]

[a] Pharmaceuticals and Medical Devices Agency, 3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013, Japan
[b] Biological Safety Research Center, National Institute of Health Sciences, 1-18-1 Kamiyoga, Setagaya-ku, Tokyo 158-8501, Japan

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ABSTRACT

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has been conducting a prospective evaluation period to validate the criteria for waiving some carcinogenicity studies in rats. Before the waiving strategy is practiced in ICH, it is crucial to elucidate whether non-neoplastic lesions are found only in 2-year rat carcinogenicity studies. To confirm possible importance of 2-year bioassays for evaluating chronic toxicity but not carcinogenicity, we retrospectively surveyed 59 pharmaceuticals approved by the Ministry of Health, Labour and Welfare (MHLW) from 2007 to 2010 in Japan for non-neoplastic lesions observed in carcinogenicity studies. Non-neoplastic histopathological lesions observed only in 2-year carcinogenicity studies but not in 6-month chronic toxicity studies using rats were compared with clinical adverse drug reactions (ADRs). Thirteen non-neoplastic lesions that may correlate with clinical ADRs were classified into three categories: Category 1, lesions not predictable from other nonclinical data except those from 2-year rat carcinogenicity studies; Category 2, lesions predictable mainly from chronic toxicity studies; Category 3, lesions predictable mainly from pharmacological actions. In the present survey, non-neoplastic lesions only found in 2-year rat carcinogenicity studies were neither significant in terms of frequency and severity nor useful for clinical risk management.

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1. Introduction

The carcinogenic potential of environmental chemicals is one of the most serious health hazards; thus, carcinogenicity of food-related or industrial chemicals has been assessed using experimental animals including rats and mice (Nishikawa, 2013). However, as for pharmaceuticals, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) in 1997 accepted the current guideline in which one of the carcinogenicity studies using rats and mice can be replaced by alternative methods such as studies using susceptible transgenic mouse, medium-term rat liver or neonatal mouse models (ICH, 1997). Recently, the S1 expert working group of ICH has further started a prospective evaluation period to validate the criteria for waiving some carcinogenicity studies in rats (ICH, 2013).

The waiver criteria are primarily based on the report by Sistare et al. (2011). In their report, they suggested that rat carcinogenicity studies could be waived in cases that lack any evidence of tumor-related histopathology, genotoxicity or hormonal perturbation because such cases retrospectively proved to be almost negative for carcinogenicity in rats, with a false-negative rate of 8%. Therefore, it is likely that the criteria named NEGCARC Rat would have promising applications to waiving rat carcinogenicity studies. Similar results have also been obtained by the analysis of data from U.S. Food and Drug Administration (FDA) or Japan Pharmaceutical Manufacturers Association (JPMA) (unpublished data). Taken

Abbreviations: ICH, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (Present name: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use.); MHLW, Ministry of Health, Labour and Welfare; ADR, adverse drug reaction; NEGCARC Rat, Negative for Endocrine, Genotoxicity, and Chronic study Associated histopathologic Risk factors for Carcinogenicity in the Rat; FDA, Food and Drug Administration; JPMA, Japan Pharmaceutical Manufacturers Association; PMDA, Pharmaceuticals and Medical Devices Agency; mTOR, mammalian target of rapamycin; JGA, Juxtaglomerular apparatus.

* Corresponding author.
E-mail address: nishikaw@nihs.go.jp (A. Nishikawa).

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together, it has been emphasized that such false-negative cases are fully interpreted by pharmacological analysis of pharmaceuticals. Thus, the weight of evidence (WOE) approach, including NEGCARC Rat, pharmacology, and other factors such as immunoresponses and the margin of exposure has been introduced. In addition, because existing analyses were all carried out retrospectively, ICH decided to validate the WOE approach prospectively, to minimize false-negative cases as much as possible.

On the other hand, apart from carcinogenicity studies, in the current ICH guideline, the minimal required duration for chronic toxicity studies using rodents is 6 months and rats are usually used for rodent chronic toxicity studies (ICH, 1998). It still remains to be validated whether the waiver for rat carcinogenicity studies can be achieved, but it is crucial to elucidate whether non-neoplastic lesions are found only in carcinogenicity studies but not in 6-month chronic toxicity studies using rats. This study was thus performed to confirm the development of such lesions by surveying the common technical documents (CTDs) for the registration and review reports of pharmaceuticals approved in Japan, especially focusing on the possible importance of 2-year bioassays for evaluating non-neoplastic lesions rather than neoplastic lesions. The CTD is structured according to the mandatory format for new drug applications in Japan (ICH, 2004).

2. Materials and methods

We retrospectively surveyed the CTDs and review reports of 59 pharmaceuticals approved by the Ministry of Health, Labour and Welfare (MHLW) from 2007 to 2010 in Japan with special attention to rat 2-year carcinogenicity studies. These data are available from the information home page of the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan (http://www.pmda.go.jp/). Pharmacological therapeutic classes of these 59 pharmaceuticals are shown in Table 1. The flow chart of the present survey is shown in Fig. 1. As the first step, we carefully selected the non-neoplastic histopathological lesions that were observed only in 2-year carcinogenicity studies but not in 6-month chronic toxicity studies using rats. For one drug without a 6-month chronic study using rats, the data for 3- and 12-month studies using rats were additionally surveyed. For this drug, non-neoplastic lesions detected in the 2-year rat carcinogenicity study were also found in a 12-month chronic toxicity study. Then, in order to consider the significance of these lesions in terms of clinical risk management, the correlation between the non-neoplastic histopathological lesions only found in carcinogenicity studies and clinical adverse drug reactions (ADRs) stated in the attachment of CTDs was comparatively analyzed. Thirteen non-neoplastic lesions caused by 10 pharmaceuticals in 2-year rat studies, excluding the lesions that obviously have no correlation with clinical ADRs, were classified into three categories: Category 1, lesions not predictable from other nonclinical data except those from the 2-year rat study, Category 2, lesions predictable mainly from chronic toxicity studies, Category 3, lesions predictable mainly from pharmacological actions. In this categorization, all chronic toxicity studies using not only rodents such as rats and mice but also nonrodents such as dogs and monkeys were also referred to.

Table 1
Pharmacotherapeutic class of 59 pharmaceuticals.

Drugs for metabolic disease	10
Drugs for circulatory organs	7
Hormone drugs	5
Chemotherapeutics	7
Antibiotic	1
Drugs for central nervous system	15
Synthetic narcotic drug	1
Drugs for digestive organs	2
Drugs for respiratory organs	2
Dermatological drug	1
Drugs for urinary and genital organs	3
Ophthalmic drugs	3
Otolaryngologeal drugs	2
Total	59

3. Results

The results are summarized in Tables 2–4. As shown in Fig. 1, among 59 pharmaceuticals surveyed, 34 induced non-neoplastic lesions only found in 2-year studies but not in 6-month studies using rats. Among the 34 pharmaceuticals, 11 were proved to have some association with clinical ADRs. Thirteen non-neoplastic lesions induced by the 11 pharmaceuticals were further analyzed in terms of their correlation with pharmacological actions and the findings in chronic toxicity studies in rodents or nonrodents.

Non-neoplastic lesions classified into Category 1 are shown in Table 2. Drug A is a voltage-dependent Ca^{2+} channel ligand approved for the therapy of neuropathic pain and fibromyalgia in Japan. Bilateral retinal atrophy found in two independent 2-year rat carcinogenicity studies may have some correlation with eye disorders labeled as clinical ADRs such as blurred vision, diplopia and visual impairment. In the case of drug A, retinal atrophy was only observed in the 2-year carcinogenicity studies, although no retinal changes were observed in the 4-, 13- or 52-week toxicity studies using rats. Thus, retinal atrophy could not be predicted from the pharmacological or other nonclinical data. Drug B is an antibacterial drug. Vacuolar changes of skeletal muscular fiber were found at medium and high doses of drug B in a 2-year rat study, which may be related to clinical ADRs such as myositis and muscle pain. Similar vacuolar changes of the cardiac muscle were found only at high doses, suggesting cardiac toxicity possibly related to a worsened general condition. Vacuolar changes of muscular fibers could not be predicted from pharmacological or the other nonclinical data. Drug C is an inhibitor of the mammalian target of rapamycin (mTOR), and atrophy and chronic inflammation of the skeletal muscle were observed in a 2-year rat study. These skeletal muscle lesions may correlate with muscle pain labeled as a clinical ADR to drug C, but could not be predicted from the pharmacological or other nonclinical data.

Table 3 shows non-neoplastic lesions classified into Category 2. Two lesions such as degeneration of the gastric mucosa and skin browning detected in a 2-year rat study of drug B may correlate with clinical ADRs such as gastroenteritis and skin color changes, respectively. These ADRs to drug B may be predictable from rat or monkey chronic studies, as shown in Table 3. Thickening of the gastric mucosa was also detected in a 2-year rat study of drug B; however, this lesion was excluded from the analysis because a similar lesion was detected in rat chronic studies of drug B. Drug D is a vasopressin V2-receptor antagonist, and liver cell hypertrophy was found in a 2-year rat study of this drug. Drug E is a dipeptigyl peptidase-4 inhibitor and vacuolar degeneration of hepatocytes was detected in a 2-year rat study of this drug. Liver dysfunction or icterus was labeled as a clinical ADR to drug D or E. Increased levels of serum alkaline phosphatase, albeit without histopathological liver changes, were detected in a dog 52-week toxicity study of drug D. In contrast to drug D, centrilobular hepatocellular hypertrophy with increased levels of serum alkaline phosphatase or aspartate aminotransferase consistently occurred in rat 4-week, 13-week and 6-month toxicity studies of drug E.

In Table 4, non-neoplastic lesions classified into Category 3 are shown. In the case of drug D, renal pelvis dilatation was also observed in a 2-year rat study of this drug, which may correlate

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