Guidance for Industry

Nonclinical Evaluation of Late Radiation Toxicity of Therapeutic Radiopharmaceuticals

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Pharmacology and Toxicology

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I. INTRODUCTION

The objective of this guidance is to provide recommendations to industry for designing nonclinical late radiation toxicity studies to determine potential late radiation effects of therapeutic radiopharmaceutical agents. The purpose of conducting nonclinical late radiation toxicity studies is to help minimize the risk of late-occurring radiation toxicities in clinical studies of therapeutic radiopharmaceuticals. Because there are other CDER guidances available for conventional nonclinical safety studies,[2] this guidance focuses solely on late radiation safety concerns that are unique to therapeutic radiopharmaceuticals. These unique safety concerns result from the risk of irreversible late radiation toxicity when these agents deliver high doses of ionizing radiation to normal organs.

This guidance is not intended for radiobiologicals (e.g., radiolabeled monoclonal antibodies). The exclusion of radiolabeled biologics is based on the lack of an established animal model for human biodistribution and the associated residence time of investigational monoclonal antibodies or other biologics. This guidance is also not intended for diagnostic radiopharmaceuticals whose low doses are not expected to elicit late radiation toxic effects.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This draft guidance has been prepared by the Late Radiation Toxicity Working Group, which includes representatives from the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] See http://www.fda.gov/cder/guidance/index.htm.

II. BACKGROUND

Therapeutic radiopharmaceuticals are typically administered systemically to treat cancer. For cancer therapy with curative intent, the radiation absorbed doses delivered by therapeutic radiopharmaceuticals are comparable to those delivered with external beam radiotherapy (XRT) and are orders of magnitude higher than doses delivered by diagnostic radiopharmaceuticals. At therapeutic doses of radiation, the late radiation toxicities commonly associated with XRT (renal, pulmonary, neurologic, late bone marrow failures, and others) can also be seen. With XRT, if the total dose given to an organ is less than its tolerance dose, the probability of symptomatic late radiation toxicity to that organ will be minimal (Perez and Brady et al. 2004). This type of toxicity should not be confused with the radiation-induced secondary malignancies for which the risk is known and accepted as unavoidable. The tolerance doses of most human organs for conventionally fractionated XRT (2 Gy once per day, 5 days per week) are known, and are routinely used to direct the safe administration of XRT. In the FDA's experience, however, there are few clinical data from which to estimate organ tolerance doses for therapeutic radiopharmaceuticals.

Organ tolerance doses for systemically administered therapeutic radiopharmaceuticals can differ significantly from the published tolerance doses for conventionally fractionated high dose rate XRT. With XRT, the dose received by an organ is determined by the geometric arrangement of the radiation beams. Organs in close proximity to the tumor are at greatest risk. In the case of systemically administered radiopharmaceuticals, the dose received by each organ is determined by the pharmacokinetics and biodistribution of the radiopharmaceutical agent. Available radiation dosimetry software programs (e.g., Medical Internal Radiation Dose (MIRDOSE) and Organ Level Internal Dose Assessment (OLINDA)) can be used to provide only rough estimates of radiation absorbed doses received by specific organs following administration of therapeutic pharmaceuticals. The accuracy of such estimates is determined by the accuracy of the pharmacokinetic data that are used in the model.

The organ tolerance doses for XRT are based on conventionally fractionated high dose rate therapy. Fractionation allows for repair of radiation damage between fractions, whereas therapeutic radiopharmaceuticals usually deliver a single dose of radiation at a low dose rate, where damage and repair of that damage occur simultaneously as competing processes. Therefore, organ tolerance doses for systemically administered therapeutic radiopharmaceuticals are not directly comparable to those for XRT. In fact, late radiation toxicity has been observed with therapeutic radiopharmaceuticals at estimated organ doses that were below the XRT tolerance doses for the target organs (Giralt and Bensinger et al. 2003). The recently described entity of low dose hypersensitivity may account for the discrepancy as could anatomic concentration of isotope not captured in the MIRDOSE (Joiner and Marples et al. 2001; Marples and Wouters et al. 2004).

Irreversible late radiation toxicities in the kidneys and bladder were observed in clinical trials with two therapeutic radiopharmaceutical agents where administered doses were estimated based upon external beam tolerance dose limits. In one study of radiopharmaceutical treatment of

multiple myeloma, 30 out of 83 patients developed renal dysfunction. Seven patients developed severe thrombotic microangiopathy (TMA) that required renal dialysis, and five of the seven patients died (Giralt and Bensinger et al. 2003). In a second clinical study of 36 patients receiving radiopharmaceutical therapy for somatostatin receptor-positive tumors, five patients developed TMA; three of whom progressed to end stage renal failure (Moll and Nickeleit et al. 2001). These toxicities were not immediately recognized as complications of the treatment because they did not begin to occur until at least 3 months after radiopharmaceutical therapy. This type of delayed onset is typical of late radiation toxicity.

Therefore, there is a need to gain additional knowledge in this area to support the safe administration of therapeutic radiopharmaceuticals to humans. Because studies in humans would be unethical, the best means to gain insight into this issue is by conducting nonclinical late radiation toxicity studies. These studies will aid in identifying organs at risk and establish a margin of safety for late radiation toxicity. As a result, these studies will help to minimize the risk of late-occurring radiation toxicities in clinical studies of therapeutic radiopharmaceuticals.

III. ACUTE VS. LATE RADIATION TOXICITY

Ionizing radiation causes injury to cells and tissues by damaging nuclear DNA (Hall 2000), although non-DNA targets are now described (Coppes and Meter et al. 2005). Most damaged cells will continue to function normally until they die while attempting to undergo mitosis. Thus the time frame in which radiation injury becomes clinically apparent is determined in part by cell turnover time (Rubin 1984). In organs with a rapid cell turnover (early reacting normal tissue) (e.g., bone marrow, epidermis, small intestine, and oropharyngeal mucosa), symptoms of radiation injury (e.g., bone marrow failure, desquamation, nausea, vomiting and diarrhea, and oral mucositis) will appear within days to weeks of an acute dose of radiation. Radiation injury to these organs is called early or acute radiation toxicity and is often self-limiting and reversible. However, in organs with a slow cell turnover rate (late responding normal tissue) (e.g., the brain, spinal cord, heart, lungs, liver, kidneys, bone, and bladder), symptoms of radiation injury (e.g., brain necrosis, paralysis, pericardial and myocardial fibrosis with left ventricular failure, interstitial pneumonitis and pulmonary fibrosis, liver or kidney failure, osteoradionecrosis, and hemorrhagic cystitis) do not occur until after a latency period of several months to years during which relatively normal organ function continues. Radiation injury to these organs is referred to as late radiation toxicity and is usually progressive and irreversible (Yaes 1992; Tubiana and Dutreix et al. 1990; Fajardo and Berthrong et al. 2001).

Since acute radiation toxicity becomes apparent within a short time period after administration, proximity in time to radiation exposure can be used as an important criterion in determining whether the radiopharmaceutical is the cause of a particular complication or adverse effect. Such toxicities will become apparent early in a clinical trial and the study can be revised or terminated, as appropriate. In contrast, late radiation toxicity in organs such as the kidneys, liver, or central nervous system (CNS) will not become apparent until months or years after treatment, necessitating longer term follow-up of treated patients.

With XRT, radiation injury is limited to organs within the radiation beams. With radiopharmaceutical therapy, the risk of radiation injury to an organ is determined by the organ's radiosensitivity and by the concentration time-activity curve of the agents in that organ or at a specific anatomical target. For example, late radiation effects can occur if the kidneys receive a significant radiation absorbed dose from radiopharmaceuticals that are removed from the systemic circulation by glomerular filtration. The kidneys are known to have a relatively low radiation tolerance dose (23 Gy for conventionally fractionated XRT); therefore, late radiation nephritis may be a dose-limiting toxicity for many therapeutic radiopharmaceuticals. Although the bladder tolerance dose is considerably higher (65 Gy), hemorrhagic cystitis can occur as a late effect unless the bladder is adequately irrigated to reduce residency time.

IV. NONCLINICAL RADIATION TOXICITY STUDIES

A. Goals

For treatment with therapeutic radiopharmaceuticals with curative intent, radiation absorbed doses comparable to doses delivered by XRT must be delivered to the tumor. Since similarly high doses may be unavoidably delivered to normal tissue, radiation toxicities commonly associated with XRT may also be seen with radiopharmaceutical therapy. Because the prescribed radioactivity is given with a very small mass dose of the carrier drug, radiation toxicity, rather than pharmacological toxicity associated with the cold (nonradioactive) drug substance (formulation), is often dose-limiting. In the past, nonclinical toxicity studies have been performed mainly with the cold formulation. Although these studies have usually shown that the no observable adverse effect levels (NOAELs) are many times the clinical mass dose, such studies assess the toxicity of the cold formulation only. Therefore, to assess the risk of late radiation toxicity in humans, it is necessary to perform late radiation toxicity studies in animals. Such studies may allow the sponsor to:

- Perform controlled experiments that are not ethically feasible in humans.
- Identify organs at risk for late radiation toxicity.
- Establish a NOAEL for late-occurring, irreversible radiation effects in an appropriate animal species, to help select the clinical doses.
- Compare the biological effects and tolerance doses of radiation delivered with radiopharmaceutical therapy to those of radiation delivered by XRT in specific organs.
- Examine the pathologic changes and possible mechanism of injury.
- Distinguish the toxicity of radiopharmaceutical therapy from that of other concomitant therapies.
- Determine the amount of organ sparing that could be obtained by fractionating the radiopharmaceutical dose.

B. Late Radiation Toxicity Nonclinical Study Design

There are challenges associated with the design and conduct of nonclinical late radiation toxicity studies. Therapeutic doses of radiopharmaceuticals require the administration of large amounts of radioactivity. The animals and animal waste will be radioactive, requiring radiation precautions to protect personnel and the general public. Precautions will also be necessary for the disposal of radioactive waste. Despite these challenges, such studies have been conducted, and are recommended to optimize dosing and thus ensure safe clinical trials and patient care. Before initiating late radiation toxicity studies, the sponsor should discuss the specifics of the study design with representatives of the Division of Medical Imaging and Radiopharmaceutical Drug Products and consider the following factors.

1. Good Laboratory Practices

Late radiation toxicity studies performed for the safety evaluation of a radiopharmaceutical drug product should be conducted in accordance with pre-existing requirements under the regulations for good laboratory practices (21 CFR part 58) and the Animal Welfare Act (7 U.S.C. 2131 et seq.).

2. Species Selection

When choosing a species, the sponsor should take into consideration the similarity in dosimetry, biodistribution, and pharmacokinetic profile of the radiopharmaceutical in the selected species and in humans. Suitable animal models to study late radiation toxicity are available. In published studies, rats (Moulder and Fish et al. 1998; Moulder and Fish 1989; Molteni and Moulder et al. 2000) and dogs (Prescott and Hoopes et al. 1990; McChesney and Gillette et al. 1989) have been shown to develop late radiation nephropathy and pulmonary fibrosis after external beam irradiation. Radiation-induced myocardial fibrosis has been shown to occur in rabbits (Fajardo and Stewart 1973) and dogs (Gavin and Gillette 1982).

3. Timing of Study

We recommend that the animal studies be scheduled to facilitate the conduct of clinical trials, including the selection of appropriate safety monitoring methods based on findings in such studies. To select the most appropriate species, human dosimetry and pharmacokinetic data using tracer doses should be obtained before initiation of the late radiation toxicity study. Ideally, the studies should be completed before the start of phase 2 dose escalation clinical trials because late radiation toxicity may not be seen in the first dose cohort until after the entire trial has been completed. In certain cases, a phase 2 clinical study can be initiated before complete submission of data from the late radiation toxicity study based on a risk-benefit analysis. However, we will evaluate the appropriateness of this approach on a case-by-case basis.

4. General Study Design

The study design should capture acute (occurring within the first few weeks after irradiation) as well as delayed (occurring after a prolonged latency) radiation effects. Clinically, late radiation toxicity is not observed until at least several months to years following the radiotherapy. In animals, late radiation toxicity usually occurs on a shorter timescale than in humans. For example, the latent period for radiation nephritis in rats ranges from 3 to 7 months. In dogs, renal dysfunction is observed by 10 months. Therefore, to obtain a reasonable estimate of the incidence of specific adverse effects, animals should be monitored for late radiation toxicity for at least 1 year post-dosing. Study duration of less than 1 year should be justified.

The preclinical study design should closely mimic the design of the anticipated clinical studies including the injected amount of radioactivity (mCi/m^2), number of doses, frequency of dosing, and dosing interval. If both single and fractionated dosing will be studied in clinical trials, a two-arm study design evaluating late radiation toxicity after single as well as fractionated dosing may be necessary. If planned radiation doses in humans will require hematopoietic growth factor support or bone marrow rescue, it may be necessary to support or rescue the irradiated animals so that they will survive comparable doses to allow for late radiation toxicity observations.

Parameters that should be monitored are similar to those evaluated in expanded single or repeat-dose toxicity studies. These include clinical observations, food consumption, body weight, ophthalmologic examination, hematology, clinical chemistry, urinalysis, and post-mortem investigations (e.g., necropsy, organ weights, macroscopic and microscopic examinations).

5. Dose Levels

Late radiation toxicity studies in animals should include at least four dose levels to identify the NOAEL and dose-related mild-to-severe late radiation toxicity. The study should also include the cold formulation (ideally, the cold isotope equivalent to the highest mass dose) as a control group to distinguish specific radiation effects from potential pharmacological effects of the cold formulation. The dose-limiting toxicities will be severe but are usually reversible (e.g., acute radiation toxicity related to the gastrointestinal tract, bone marrow). Therefore, the highest dose selected should produce acute radiation toxicity. This dose should be at least twice the maximum planned human dose or radiation tolerance dose for the critical organ (TD5/5 external beam radiation) identified as a possible dose-limiting factor in clinical studies. The dose-multiples should be expressed in terms of body surface area (mCi/m^2) and radiation absorbed dose to the critical organs, when critical organs have been identified. The number of animals in each group should be sufficient to ensure survival of an adequate number to perform proper analysis at the completion of study.

6. Clinical Pathology

Hematology, urinalysis, and clinical chemistries should be performed pre-dosing, 2 weeks post-dosing, then once every 3 months afterward and at termination. In addition to a standard battery of hematology and clinical chemistry parameters, the study should also include the assessment of

relevant biomarkers, if available, to identify late radiation toxicity for the target organ. For example, urinary glutathione-S-transferase isoenzyme levels can be monitored in addition to blood urea nitrogen and creatinine levels as markers for renal injury. It is recommended that the study design be developed in consultation with the FDA to ensure that appropriate long-term toxicity indices are monitored.

7. Necropsy and Histopathology

Necropsy, including organ weights and macroscopic examination of various organs, should be performed for all animals in the study, including those that died during the study observation period. Detailed histopathologic/microscopic evaluation should be performed at termination.

V. CONCLUSIONS

Late radiation toxicity has been observed where doses of radiopharmaceuticals were determined based on external beam organ tolerance dose limits. Therefore, there is clearly a need to gain additional knowledge in this area to support the safe administration of these products. Because studies in humans would be unethical, the best means to gain insight into the potential irreversible late radiation toxicity with these products is by conducting nonclinical toxicity studies. These studies will aid in identifying at-risk organs, establish a margin of safety for late radiation toxicity, quantify potential organ sparing when dose fractionation is used, and compare organ tolerance doses for radiopharmaceutical therapy to tolerance doses for fractionated external beam treatment.

Late radiation toxicity protocols should be submitted to the Agency for review before the studies are initiated. Ideally, radiation toxicity studies in animals should be completed and analyzed before phase 2 dose escalation toxicity studies are initiated in patients. Until we have a better understanding of tolerance doses for radiopharmaceutical therapy, the safest way to proceed is to prescribe doses in mCi/m^2 to individualize patient doses by body surface area. Since pharmacokinetic parameters for some of these agents have been known to vary significantly from patient to patient, before any patient is treated, biodistribution and pharmacokinetic data should be obtained for that individual patient using quantitative gamma camera imaging with diagnostic doses of the therapeutic agent where possible. These data should be used to estimate radiation absorbed doses to each individual patient's critical organs using MIRDOSE-3 or OLINDA (or other adequate) dosimetry software. For patients who would receive unusually high doses to critical organs, it may be necessary to decrease the injected activity, or exclude the patient from the study.

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GLOSSARY

Acute Radiation Syndrome — The symptoms, when taken together, characterize a person suffering from the effects of intense radiation. The effects occur within hours or days.

Dose Fractionation — A method of administering therapeutic radiation in which relatively small doses are given daily or at longer intervals.

Early Effects (of radiation exposure) — Effects that appear within 60 days of an acute exposure.

Late Effects (of radiation exposure) — Effects that appear 60 days or more following an acute exposure.

Radiation Absorbed Dose — The energy imparted to matter by ionizing radiation per unit mass of irradiated material at the place of interest. In SI units, the unit of radiation absorbed dose is the Gray (Gy), which is 1 J/Kg. One Gy equals 100 rads.

Radionuclide — Any radioactive isotope of an element.

Radiosensitivity — Relative susceptibility of cells, tissues, organs, organisms, or any living substance to the injurious action of radiation. Radiosensitivity and its antonym, radioresistance, are currently used in a comparative sense, rather than in an absolute one.

Therapeutic Radiopharmaceutical — A radiopharmaceutical drug product or radiobiological that is intended for use in the treatment of cancer in humans and that contains a radioactive isotope which exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear radiation. The isotopes used in therapeutic radiopharmaceuticals are usually beta emitters whereas the isotopes used in diagnostic radiopharmaceuticals are gamma emitters. Therapeutic radiopharmaceuticals are given in much higher activities and deliver much higher radiation absorbed doses than diagnostic radiopharmaceuticals.