Relevance of External Beam Dose–Response Relationships to Kidney Toxicity Associated with Radionuclide Therapy

Joseph O’Donoghue
Department of Medical Physics, Memorial Sloan-Kettering Cancer Center, New York, NY

ABSTRACT

The importance of the kidney as a dose-limiting organ is likely to increase as smaller molecular vectors and radiometals become more commonly used in targeted radionuclide therapy. Data derived from kidney irradiation by external-beam therapy (XRT) indicate that the kidney is radiosensitive. The features of radiation nephropathy seen post-treatment appear similar between local XRT, total-body irradiation (TBI), and radionuclide therapy. For uniform kidney irradiation, tolerance doses appear to be approximately 15–17 Gy in 2 Gy fractions for local XRT and probably less than this (<12 Gy in 2 Gy fractions) when radiation is delivered systemically as TBI in the context of bone marrow transplant protocols. Animal studies indicate that the linear quadratic (LQ) model with an α/β parameter of 1.5–3 Gy seems to adequately describe the XRT fractionation sensitivity of kidney for doses per fraction down to approximately 1 Gy, but may underestimate the effectiveness of fraction sizes less than this. Animal studies have also clarified the dose-dependency of the time to expression of radiation nephropathy and have indicated that radiation nephropathy may be alleviated by pharmacological means.

Key words: radiation nephropathy, dose–response, external beam, animal models

INTRODUCTION

There is a growing realization that the risk of radiation nephropathy is becoming a major consideration for targeted radionuclide therapy. This is due to a combination of factors that include:

1. The increasing use of smaller molecular vectors that are preferentially cleared by the renal route, possibly coupled with some degree of kidney retention.

2. The use of novel therapeutic radionuclides, especially radiometals such as ^188^Ho and ^213^Bi.

3. The general increase in therapeutic intensity afforded by the use of bone marrow rescue. Second-organ toxicities may be cardiopulmonary for high molecular weight vectors, such as intact IgG, but are more likely to be renal for smaller molecular vectors.

The risk of radiation nephropathy is an important consideration in external-beam radiotherapy (XRT), although historical experience has conditioned current practice to the extent that it is now rarely seen. However, the introduction of novel techniques generally requires a reassessment of this situation. One important lesson from the past is that relative safety is the child of bitter experience.
In this short review, the relevance of the external-beam radiotherapy experience to molecularly targeted radionuclide therapy will be discussed. This is not meant to be a comprehensive review, but rather a selection of observations and theoretical considerations that illustrate relevant aspects of renal toxicity produced by both radiation modalities.

Radiation Nephropathy

The classical symptoms of radiation nephropathy were first classified by Luxton4–3 into four clinical categories of acute radiation nephritis, chronic radiation nephritis, benign hypertension, and late malignant hypertension, and late malignant hypertension, and proteinuria. These syndromes become manifest over varying timescales post-irradiation, ranging from 6 to 12 months for acute radiation nephritis up to many years post-irradiation for chronic radiation nephritis, late malignant hypertension, and proteinuria. The nature of radiation injury in the kidney is complex,4 and several cell populations and/or structures seem to be at risk. Although both glomerular and tubular damage is observed, it is believed that glomerular injury is the initial event, with the later manifestation of damage to other renal components, to some extent, consequential to this.

The features of the nephropathy caused by radionuclide therapy appear similar to those of “classical” radiation nephropathy. They consist of some, or all, of the following: reduction in renal hemodynamics, increase in serum creatinine and blood urea nitrogen (BUN), anemia, proteinuria, hypertension, and, at a microscopic level, thrombotic microangiopathy.

Sources of data on radiation nephropathy include clinical studies that featured un- or bilateral kidney irradiation delivered either as local external-beam radiotherapy (XRT) or as systemic external-beam total-body irradiation (TBI). Together with these clinical data, there are a number of studies on experimental animals that have examined the radiation response of the kidney and whether this may be modified by pharmacological means.

Renal Tolerance to Local XRT

In their review of the tolerance doses of normal tissues to radiation, Emani et al.5 suggest values of 23 Gy for TD50S and 28 Gy for TD95S for whole-kidney irradiation. These figures are estimates of the total radiation dose delivered in approximately 2 Gy fractions that will produce excessive toxicity in 5% or 50% of patients within 5 years. The quoted values are largely determined from an early clinical study6 that featured whole-abdominal irradiation in the treatment of seminoma testis. In this study, a number of conformations of 250 kVp X-rays fields were investigated with the aim of improving the uniformity of the abdominal dose distribution. One particular treatment conformation produced a high incidence of radiation nephropathy. In this case, the absorbed dose to both kidneys was close to uniform, with estimated average values of either 2300 r or 2800 r. Depending on the prescription. The doses were quoted in r (roentgen), a historical unit of radiation exposure. Treatments were delivered using daily fractionation (6 fractions per week) over periods of 4–5 weeks. Luxton7 concluded that “where it is imperative to include the whole of both kidneys within the irradiated volume in a patient with malignant disease, a dose of 2300 r over 5 weeks may be acceptable.”

A number of factors must be considered when interpreting these data. These include the conversion from the roentgen unit of exposure to the absorbed dose, the uncertainties of kidney visualization and dose estimation, the then-current technology, and the fractionation scheme used. However, if the data is taken at face value and an approximate conversion factor (1 r ≈ 0.01 Gy) is used, the equivalent tolerance dose in 2 Gy fractions can be estimated using the linear quadratic (LQ) model. For a kidney α/β ratio of between 2–3 Gy, the 2 Gy-equivalent tolerance dose (corresponding to 23 Gy in 24–30 fractions) is 16–18 Gy.

Fig. 1 shows a dose-response curve for symptomatic radiation nephropathy reprinted from Cassady’s 1995 review.8 The data included in this figure come from a variety of studies of un- or bilateral kidney irradiation, with differing clinical endpoints and follow-up times making direct intercomparisons difficult. Cassady stated that “a threshold dose of = 15.0 Gy delivered with conventional fractionation (in the absence of interactive drugs and underlying renal disease) appears reasonable, while radiation doses of more than 25.0–30.0 Gy to the total renal mass are likely to eliminate useful renal function in patients followed for sufficiently long periods of time.”
Renal Tolerance Following BMT

Renal impairment is a relatively common complication following bone marrow transplantation (BMT).\(^8,9\) BMT nephropathy seems to be morphologically and functionally equivalent to “classical” radiation nephropathy. Although there may be a number of contributory factors, including immunological factors and the use of nephrotoxic chemotherapy, the occurrence of BMT nephropathy is highly influenced by the use of total-body irradiation (TBI) in a dose-dependent manner. This was illustrated by the study of Lawton et al.,\(^10\) which examined the impact of varying levels of renal shielding on the incidence of BMT nephropathy. In this study, patients received 14 Gy TBI in 9 fractions (3 fractions per day for 3 days, with at least 4 hours between fractions). Out of 157 evaluable patients, 72 had no renal shielding (i.e., kidney dose \(\frac{P}{H1000} \approx 14.0\) Gy), 68 had 15% renal shielding (i.e., kidney dose \(\frac{P}{H1000} \approx 11.9\) Gy), and 17 patients had 30% renal shielding (i.e., kidney dose \(\frac{P}{H1000} \approx 9.8\) Gy). The incidence of BMT nephropathy as a function of time post-treatment is shown in Fig. 2 and indicates a clear demarcation between the different dose groups. Because of the relatively short time between fractions, it is possible that the repair of kidney radiation damage was incomplete.

Incomplete repair can be addressed using the
LQ model. If we assume a kidney α/β ratio of 2.5 Gy, a half-time of 2 hours for (monoexponential) repair, and exactly 4 hours between fractions, it can be calculated that the 2 Gy-equivalent doses, corresponding to 14, 11.9, and 9.8 Gy, are 14.4 Gy, 11.4 Gy and 8.7 Gy, respectively.

Qualitatively similar results were reported by Miralbell11 in a patient group who received varying doses of TBI prior to allogeneic BMT. The 18-month probabilities of renal dysfunction-free survival were 95%, 74%, and 55% for the patients conditioned with 10, 12, and 13.5 Gy, respectively. However, renal dysfunction after allogeneic BMT was also strongly related to the presence of graft-versus-host disease (GvHD). These authors recommended the use of renal shielding for TBI doses greater than 12 Gy and that kidney doses greater than 10 Gy should be avoided in patients who are at high risk of developing GvHD. In contrast to these data, the recent report of Miralbell et al. found a higher rate of renal dysfunction 4 months post-treatment in patients who had partial kidney shielding to 10 Gy, compared to those who received an unshielded TBI dose of 12 Gy.12 The reasons for these apparently paradoxical findings are not clear. One possibility, suggested by the authors, is that potentially nephrotoxic contrast agents that were used in the procedure for designing kidney shields were responsible.

Animal Model Systems
The radiation response of kidney in terms of fractionation sensitivity, repair kinetics, and the dose-dependency of time to expression of radiation injury have been studied in animal model systems.

Assays of Nephropathy
In animal models, radiation nephropathy is generally defined using measurements of 51Cr-EDTA retention in blood, hematocrit (%Hct), blood urea nitrogen (BUN), and proteinuria in terms of the ratio of urinary protein to urinary creatinine (UP/UC). It has been reported that, for similar radiation doses, 51Cr-EDTA will detect renal damage earlier than BUN and that %Hct will detect renal damage at lower radiation doses than either 51Cr-EDTA or BUN.13,14 It has also been observed in rodents that radiation-induced proteinuria becomes apparent before any significant decrease in renal function.15,16

Fractionation Sensitivity
Joiner and Johns reported a study of bilateral kidney irradiation in mice with renal function assayed by 51Cr-EDTA blood clearance.17 Because of the very small fraction sizes investigated in the experiment, a neutron "top-up" dose was used to avoid delivering an excessive number of fractions. Fig. 3 illustrates the relationship between total dose and dose per fraction calculated to achieve an equivalent biological response (iso-effect curve) derived from the combination of these data with results of earlier experiments with larger fraction sizes. The data are adequately described by the LQ model with an α/β ratio of 2.2 Gy for fraction sizes down to approximately 1 Gy. However, as the fraction size decreases below 1 Gy, the data deviates more and more from the LQ curve. Thus, the LQ model appeared to describe the kidney iso-effect relationship for fraction sizes of 1 Gy or more, but underestimated the biological effectiveness of fraction sizes less than 1 Gy.

Other experiments in rodents with fraction sizes of greater than 1 Gy are broadly supportive of the use of an α/β ratio of 1.5–3 Gy for radiation nephropathy.18–20

---

**Figure 3.** Relationship between total dose and dose per fraction calculated to achieve equivalent renal damage. The data are adequately described by the LQ model with an α/β ratio of 2.2 Gy for fraction sizes down to approximately 1 Gy. As the fraction size decreases below 1 Gy, the data deviates more and more from the LQ curve, (adapted from ref. 17 with permission).
Kinetics of Radiation Damage Repair in Kidney

In a subsequent paper, Joiner et al. examined the kinetics of repair of radiation damage in mouse kidney. The kidneys were subjected to bilateral irradiation and a neutron "top-up" dose was used as required. Renal function was assessed 16–45 weeks postirradiation, and data based on two different biological assays of renal function (51Cr-EDTA clearance and reduction in hematocrit) were combined. The results of this experiment are shown in Fig. 4. In this figure, the y-axis represents the biologically effective dose (BED), which is a measure of radiation damage. As the time between fractions was increased, the amount of radiation damage decreased. The kinetics of this repair process were adequately described by a monoexponential function, with an estimated half-time of approximately 1.3 hours. There was no difference in the rate of repair following doses per fraction of 2 or 7 Gy, and there was no evidence for multiphasic repair.

Other studies using functional assays of radiation nephropathy in rodents are broadly supportive of the repair of radiation damage in kidney, having a characteristic half-time of around 1–2 hours. However, analysis of an in vitro assay of normal kidney colony-forming cells following in vivo irradiation suggests that a portion of the radiation damage in the kidney may be repaired at a relatively slow rate.

Dose-Dependent Time to Expression of Radiation Damage

Another significant finding of experimental investigations of radiation nephropathy is that the time to expression of functional renal damage is dose-dependent, with shorter times corresponding to larger doses. This is illustrated in Fig. 5.

These data represent the time course of renal impairment following bilateral irradiation of mouse kidneys with 20 fractions of 250 kV X-rays to total doses of between 24–50 Gy. Renal function was assessed every 4 weeks by 51Cr-EDTA blood clearance. The mean times to expression of "moderate to severe" damage, defined as a residual plasma 51Cr-EDTA level of 4%, were 74, 54, and 42 weeks for 20 fractions of 1.2, 1.6, and 2.0 Gy, respectively, reducing to <30 weeks for higher total doses.

Significance of the Dose-Dependent Time to Expression of Radiation Damage

The observation of dose-dependency in the temporal development of renal functional impairment is inconsistent with the hypothesis that the kidney has a hierarchical tissue organization. A hierarchical, or H-type, organization refers to a situation where there is a distinct population of clonogenic, but functionally incompetent, stem cells that feed into a maturing compartment with limited functional capacity and proliferative potential. This finally supplies a fully functional
compartment with no ability for division. Organ systems, such as the gastrointestinal epithelium or the hematopoietic system, have this type of structure. The response of an H-type system to radiation insult is characterized by a progressive diminution of functional cell number until a nadir is reached, followed by compensatory accelerated proliferation. The time to expression of radiation damage is primarily determined by the lifetime of functional cells and is relatively insensitive to dose.

Rather than a H-type model, the behavior of the irradiated kidney seems to be better described by a “flexible,” or F-type, model of tissue organization. An F-type system consists of a cell population that is not only functionally competent but also capable of proliferation. Routine cellular turnover involves the loss of cells, capable of both division and function, at the end of their natural lifetime. In an unirradiated tissue, the demand for compensatory proliferation is relatively weak, and replacement cells are produced by a steady-state—but indolent—turnover. Exposure to ionizing radiation renders a dose-dependent proportion of the cell population nonviable. As functional cells are lost from the tissue because of normal physiological factors, some of the remaining cells attempt to divide in order to maintain tissue function. Latent radiation damage may then be expressed as abortive mitoses. Depending on the amount of latent radiation damage present, this may lead to a potentially catastrophic “avalanche” of cell death as more and more cells are recruited to divide. For an F-type organization, the time to expression of radiation damage is inversely dose-dependent.

Modifiers of Radiation Response

One of the interesting aspects of the F-type model of the kidney is that radiation damage may remain latent in the form of “doomed” cells that continue to fulfill a physiological function and will only become expressed if these cells are stimulated to proliferate. The occurrence of mechanical damage, which may trigger proliferative regeneration, may, therefore, act to potentiate the radiation damage. Conversely, steps that minimize mechanical damage to the kidney or, in some other way, reduce the amount of cellular proliferation could protect both the tissue from the expression of radiation damage and the host from the consequences of the loss of tissue function.

There have been a number of experimental studies of purportive chemical modifiers of radiation response in kidney. Most of these studies have produced essentially negative results and are summarized in Table 1. However, some studies have indeed shown a significant sparing of renal damage.

Moulder et al. have reviewed their experience of using the angiotensin-converting enzyme (ACE) inhibitor captopril and an angiotensin II (AII) receptor blocker (designated L-158,809) for the prevention and treatment of radiation damage.

### Table 1. Experimental Studies on Purportive Chemical Modifiers of Radiation Response in the Kidney

<table>
<thead>
<tr>
<th>Agent</th>
<th>Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylsalicylic-acid</td>
<td>Initial suggestion of protection, subsequent report no significant effect</td>
<td>[28] [29]</td>
</tr>
<tr>
<td>platelet ADP receptor antagonist (clopidogrel)</td>
<td>No effect</td>
<td>[30]</td>
</tr>
<tr>
<td>Superoxide dismutase, catalase</td>
<td>No reversal of radiation-induced proteinuria</td>
<td>[15]</td>
</tr>
<tr>
<td>Low-dose chemo</td>
<td></td>
<td>[31]</td>
</tr>
<tr>
<td>BCNU</td>
<td>Sensitization</td>
<td></td>
</tr>
<tr>
<td>Mitomycin</td>
<td>Minimal effect</td>
<td></td>
</tr>
<tr>
<td>Angiotensin II</td>
<td>Exacerbation of renal toxicity</td>
<td>[32]</td>
</tr>
<tr>
<td>All-trans retinoic acid</td>
<td>Exacerbation of renal toxicity</td>
<td>[33]</td>
</tr>
</tbody>
</table>

*These experimental studies on purportive chemical modifiers of radiation response in the kidney have produced essentially negative results.*
nephropathy. Fig. 6 shows the effects of these agents in terms of the prevention of radiation nephropathy in rats receiving 17 or 20 Gy TBI prior to bone marrow rescue. The drugs were delivered through the drinking water, starting 9 days before irradiation and maintained throughout the experimental period. Animals receiving captopril or AII blocker had significantly better renal function, compared to control animals that did not receive drug therapy. Histopathologic analysis of kidney specimens indicated that the AII blocker was more effective in preventing the lesions characteristic of nephropathy than the ACE inhibitor. These agents were also shown to be effective in the treatment of preexisting radiation nephropathy. Fig. 7 shows a similar set of results, but this time the drug treatments were started 6 months after irradiation in animals with elevated BUN. These experimental results are very encouraging. A placebo-controlled trial of captopril to prevent BMT nephropathy in adults is now underway, and there are preliminary indications that radiation nephropathy in human patients may be alleviated by the use of AII blockers.26

Applicability of the XRT Experience to Radionuclide Therapy

The question of how applicable is the XRT experience to radionuclide therapy is of critical importance. Unfortunately, it is also difficult to answer with any degree of certainty and much of the following discussion is speculative.

It would seem that a useful rule of thumb is to use the appropriate tolerance dose derived from XRT as a threshold that radionuclide therapy should aim not to exceed. In most cases, the value for local kidney irradiation (15–17 Gy in 2 Gy fractions) would be appropriate. This is because the lower threshold, of approximately 12 Gy in 2 Gy fractions, suggested by the TBI data refers to a context of compromised immunological function, the use of bone marrow rescue, and the likelihood of nephrotoxic chemotherapy that is untypical for radionuclide therapy. Of course, if radionuclide therapy is being contemplated in the latter context, it would be more appropriate to choose the lower threshold value.

A further consideration is how these XRT-based tolerance doses translate into the protracted low dose-rate irradiations typical of radionuclide therapy. This is the realm of radiobiological models, the most commonly used of which is the LQ model. Animal data suggest the LQ model may underestimate the effectiveness of doses per fraction less than 1 Gy in producing radiation nephropathy.17 By analogy, it may, therefore, underestimate the effectiveness of low dose-rate irradiation. However, there are, at present, no reliable data from which to draw a conclusion.

If we accept the LQ model at face value, then the influence of the rate of repair on biological effectiveness can be examined. In the special case of an exponentially decreasing dose-rate that de-
livers a dose D with an effective half-life, $T_d$, it can be shown that the radiobiologically equivalent XRT fraction size is just $D(T_r/(T_d + T_r))$, where $T_r$ is the half-time for repair. This indicates that what determines the biological effectiveness of a protracted dose-rate are the comparative rates of clearance and repair. If the rate of repair is slow (i.e., $T_r$ is long), the effective fraction size will be greater, and there will be less sparing. If only a portion of renal damage is repaired at a relatively slow rate, as suggested by the analysis of Millar, then there will be some enhancement of the biological effect but not so much as if all the repair occurred slowly.

RESULTS

There are significant differences between kidney irradiation by external beam and systemically distributed radionuclides. The dose distribution for external beam is “simple.” In the case of TBI, the dose to the kidney is fairly uniform and for local XRT any dosimetric nonuniformities that exist are purely spatial, as they are related to the geometry of the radiation fields and not to biological factors.

For radionuclide therapy, dose distributions are more complex in terms of both temporal and spatial variability. In addition, for radionuclide therapy, dosimetric nonuniformities are not just spatio-temporal but are also related to renal function. Radionuclide clearance and retention in the kidney depends on its chemical form and the molecular weight of the vector. There may be high, but transient, concentrations coupled with the possibility of more prolonged retention in the various kidney subregions. This will give rise to a nonuniform distribution of absorbed dose and dose-rate determined by the interaction between the emission range and half-life of the radionuclide and the time-dependent biodistribution. The intrarenal biodistribution and kinetics are not necessarily fixed and may be amenable to modification—for example, by the infusion of basic amino acids. Methodologies such as this may be useful in the reduction of kidney dose and should be pursued.

The fundamental requirement for a rational assessment of radiation nephropathy is accurate dosimetry. Certainly, without accurate dosimetry, the use of radiobiological models is of little value. The increasing availability of computed tomography–positron emission tomography (CT-PET) in the clinic will facilitate detailed subregional biodistribution data to be generated. In order to properly understand the development of radiation nephropathy, studies of the time course of the intrarenal distribution of activity will also be required. However, this may be investigated more systematically in complementary animal models studies. In addition, the availability of the new MIRD Pamphlet No. 19 on multiregional kidney models will be a major benefit. Another important task will be to develop and validate methodologies for assessing renal function that can give advance notice of the risk of renal failure. This will be especially important if methods of treating radiation nephropathy prove to be effective.

Complementary to clinical studies, it would appear that a major effort will be required in animal model systems, with the aim of understanding the relationship between the spatio-temporal distribution of the absorbed dose and the development of renal toxicity. In this endeavor, the experiences acquired from animal studies of kidney irradiation by XRT will be a useful guide. Animal model studies will require high-resolution imaging with dedicated PET and/or single photon emission computed tomography (SPECT) systems coupled with detailed autoradiographic and histological studies. Together with the development of animal models of kidney dosimetry, it will be useful to develop and validate image-based assays of renal function to complement the traditional assays.

CONCLUSIONS

The summary of key points includes:

From clinical studies in humans:

1. The kidney is radiosensitive and will become of increasing importance as a dose-limiting organ for radionuclide therapy.
2. The morphological and functional features of renal toxicity are similar between local external-beam radiotherapy (XRT), total body irradiation (TBI), and radionuclide therapy.
3. The “tolerance” dose for radiation nephropathy is probably around 15–17 Gy in 2 Gy fractions for XRT.
4. The “tolerance” dose for TBI when given with bone marrow rescue appears to be less than for XRT, and is probably approximately 12 Gy in 2 Gy fractions.
From experimental studies in rodents:

5. The linear quadratic (LQ) model seems to adequately describe kidney response to fractionated irradiation for doses greater than approximately 1 Gy, but is not reliable for doses less than this.

6. The α/β parameter for radiation nephropathy is in the range of 1.5–3 Gy.

7. Repair of radiation damage in kidney seems to be adequately described by a monoeponential process, with a half-time of 1–2 hours.

8. There is a dose-dependent time to expression of radiation injury in kidney. The greater the dose, the shorter the time to expression.

9. To some extent, radiation nephropathy may be both preventable and treatable by pharmacological means. The best current candidate appears to be the angiotensin II (AII) receptor blocker.

REFERENCES


