Summary and Perspectives on Kidney Dose–Response to Radionuclide Therapy

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INTRODUCTION

The manuscripts included in this special issue of Cancer Biotherapy & Radiopharmaceuticals highlight current data and theoretical foundations regarding dose–response relationships related to radionuclide therapy kidney toxicity. With the use of the kidney dosimetry model presented in MIRD 19,¹ these experimental and clinical data, when correlated with accurate regional dose information, may provide the improvements in predictive models necessary for clinical trial design. Some fundamental findings from the current proceedings may be summarized:

Observation 1

Kidney toxicity has been observed in several experimental models and in patients after the administration of several radiopharmaceutical agents.

Observation 2

Patient and animal model data show a varying degree of nonuniformity of uptake and retention of radiopharmaceuticals in the kidney suborgan structure.

Observation 3

The relationship between the total dose, dose rate, and the nonuniformity of activity deposition in the context of the underlying biology, is complex. In order to develop more effective predictive models for these complex patterns of dose deposition, more direct experimental studies—using radionuclide therapeutic agents—will be necessary to confirm model predictions.

Specifically, will it be useful and predictive to define these parameters for a patient population independent of the carrier and radionuclide, or will it be necessary to directly measure them for each patient, radionuclide, and carrier type? This kind of question underscores a larger concern of how the term “patient-specific data” is practically and constructively defined. With respect to the experimental data and radiobiological predictive models discussed by the authors in this compilation, the following queries may be valuable in confirming the applicability of new data:

1. Is it sufficient to measure the radiosensitivity of a specific organ to external-beam radiation (EBRT), or is it necessary to have a specific knowledge of the organ sensitivity of an individual patient to the administered radioactive drug?

2. Can a value of the alpha/beta ratio for the human kidney be adapted from the external-
beam literature, or must it be directly measured from a specific patient undergoing radionuclide therapy? Is the same true for tissue repair times? (3) Can we measure the relative nonuniformity of kidney uptake for a class of radiolabeled agents in patients, or must the specific radiopharmaceutical distribution be measured in all patients?

In the current paper by Green et al., (pp. 371–377) Figs. 1A and 1B show a highly heterogeneous distribution of radiolabeled carrier over time. From this, they are able to compute a region-specific dose-rate profile. Higher dose rates and potentially total-dose deposition corresponds to areas in the cortex of the kidney, which contain several radiobiologically sensitive elements and can selectively affect kidney performance. Subsequently, if these data were translated to a clinical setting, the calculation of a uniform dose to the kidney would be misleading and may lead to an underestimate of dose in a dose–response relationship when compared to the external-beam experience. Clinical data presented and reviewed2–5 showed selective suborgan uptake, as indicated through a variety of in vivo and ex vivo imaging methods. However, these complete, and spatially definitive, data sets are not readily acquired through the traditional single-photon emission computed tomography (SPECT) single-time point-imaging acquisitions associated with most clinical trials. Perhaps as more positron emission tomography (PET) agents become available, the increased resolution to the subcentimeter voxel level may improve the diagnostic acquisition of suborgan structures in the kidney such that a more accurate dosimetry can be obtained.

Arguably, when these data at the suborgan level have not been available for patient therapeutic applications and/or the data collected from a single SPECT imaging session does not indicate gross heterogeneous uptake in the kidney, a uniform activity distribution over time may be assumed, by default. The dosimetry calculation methods in this case for the kidney are still not straightforward by any standard. Investigators must first decide how the time-activity curves for the kidney used to derive dose estimates are to be obtained. Namely, should one rely on the modeling methods described in ICRP 536 or base the dose estimates on image quantitation through the use of the conjugate view method, as outlined in MIRD 167? And furthermore, what does the investigator conclude when dose estimates obtained by these two methods do not substantially agree?

Moving forward with the simplest scenario, if we arrive at a dose estimate to the kidney which is uniform based on clinical imaging data of sufficient macroscopic resolution, authors Dale (pp. 363–370) and O’Donoghue (pp. 378–387) have provided us with some tools that may account for the rate of dose deposition. As indicated by both Brietz (pp. 359–362) and O’Donoghue (pp. 378–387), a substantial body of data exists for the scoring of kidney toxicity by both fractionated external-beam data and that associated with total-body irradiation (TBI) for conditioning regimes used in bone marrow transplant. These data indicate that for radiation given in a shorter time interval, as in the case of TBI, the dose for kidney tolerance (TD5/5) is reduced to 14 Gy or less, compared to the widely accepted 20–23 Gy for regular fractionated EBRT.8 The linear quadratic (LQ) model predicts this result with reasonable accuracy, according to Dale (pp. 363–370) and O’Donoghue’s (pp. 378–387) manuscripts as presented in this compendium.

In a similar exercise to that reported by Dale (Table 1, p. 368), the use of the LQ model can assist us in understanding the effects on response when the time interval over which the dose given uniformly to the kidney is reduced from several weeks to hours. Using the following three fractionation schemes to deliver a dose of 18 Gy to both kidneys:

(1) Total delivery time of 5 hours for 95% of the dose—Corresponds to rapid transit of activity and limited kidney retention of this activity delivered from exponentially decaying radionuclide therapy.
(2) Total delivery time of 100 hours for 95% of the dose—Corresponds to relatively slow transit of activity and high localized, but uniform retention of activity in the kidney delivered from exponentially decaying radionuclide therapy.
(3) Total delivery time of 13 days for fractionated EBRT—2 Gy per fraction for a total of 9 fractions to the kidneys.

Using the LQ model assumptions similar to what was outlined by Dale (p. 366) and O’Donoghue (pp. 378–387):

Given—$T_{1/2}$ repair = 1 hour
Corresponding results for the above examples are:

1. For 5-hour interval—RE—2.6; BED = 46.5 Gy
2. For 100-hour interval—RE—1.1; BED = 20.0 Gy
3. By EBRT—9 Fx at 2.0 Gy/Fx; RE—1.8; BED = 33.0 Gy

Hence, from the application of these modeling methods, the resultant predictions for dose response to the kidney would be:

1. Based on the BED calculations, 18 Gy given over just 5 hours will show an increase in the risk of radiation-induced nephrotoxicity, compared to the EBRT—suggested limit of 22 Gy (given in standard 2 Gy fractions—BED—40.3 Gy).
2. Conversely, 18 Gy given over 100 hours to the kidney by uniform exponentially decaying radionuclide therapy would result in an acceptable level of toxicity, compared to EBRT standards.

These calculations and dose-limiting toxicity values may differ somewhat from the results quoted by Dale (p. 368) and O’Donoghue (pp. 379–380) in this issue, but the overall conclusions stated here would remain the same. Specifically, requiring 95% of the radiation dose (18 Gy) to be given in just a 5-hour period in the first example shown above would correspond to an IDR much greater than the values considered in Table 1 of the Dale paper (p. 368). Similarly, if most of the radiation is given in a period of 100 hours from an exponentially decaying dose rate source, a much lower IDR would be computed and, therefore, more sparing of normal tissue would result. In addition, it is recognized that a reduction in the tolerance dose for the kidney, as asserted by O’Donoghue (p. 379), may well be true, especially in view of the onset of additional late effects past 5 years, as noted by Cassady.

CONCLUSIONS

Based on the oral presentations at the MIRD Continuing Education Sessions at the 2003 National Meeting of Society of Nuclear Medicine and the manuscripts presented in these proceedings, the following summary statements and extrapolations for future work can be made:

1. Nonuniformity of dose deposition may increase or decrease the risk of toxicity, depending on where the dose is deposited in the kidney.
2. For uniform distribution of a dose to the kidney, the dose-rate effects observed from the external-beam experience may be applicable to radionuclide therapy through the use of the LQ model modified with an incomplete repair term for the exponentially decaying dose rate. This remains to be confirmed by experimental and clinical dose-response data generated for radionuclide therapy.
3. Assuming proximal convoluted tubules are predominately located in the cortex region of the kidney and are associated with a greater radiobiological sensitivity—the functional subunit (FSU) and BED approaches, coupled with MIRD 19 multiregion dosimetry, may lead to better predictive modeling for kidney-dose response.

REFERENCES