Clinical Aspects of Radiation Nephropathy

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ABSTRACT

Small radiolabeled molecules are finding increasing clinical use for targeted radionuclide therapy. With the administration of radiolabeled small molecules, the bone marrow is not necessarily the first organ to show radiation toxicity. Rapid excretion of radioactivity through the urinary tract and the retention of radiolabeled small-protein molecules in the kidneys may expose the kidneys to radiation sufficient enough to cause toxicity—and in clinical trials, radiation toxicity of the urinary tract has become clinically relevant. The cells of the kidneys are slowly repairing cells; thus, the radiation toxicity may not be manifest for several months. The clinical and pathological features associated with radiation nephropathy, and issues particular to radiation nephropathy following targeted radionuclide therapy, are described here.

Key words: radiation nephropathy, radionuclide therapy, thrombo-microangiopathy

INTRODUCTION

The occurrence of kidney dysfunction following external radiation has been recognized for a hundred years. It initially was described in 1904, by Baerman. In 1962, Luxton proposed guidelines to limit radiation exposure in terms of the absorbed dose from fractionated external-beam therapy. The introduction of different dosing regimens for total-body irradiation (TBI)—for example, up to 14 Gy delivered within 4 days or less—and the use of internal radiation from high-dose-targeted radionuclide therapy, have raised questions on the tolerance of the kidneys to radiation delivered over a shorter period of time. Kidney dysfunction has been attributed to radiation exposure from TBI prior to bone marrow transplant (BMT). The recent introduction of targeted radionuclide therapy has raised new questions about the radiation-absorbed dose to the kidney, and other factors that may contribute to radiation nephropathy following this newer radiotherapy modality.

Clinical Presentation of Radiation Nephropathy

The term radiation nephropathy is more appropriate than the older term radiation nephritis, because, histologically there is no evidence of inflammation in the kidneys. The clinical presentation of radiation nephropathy falls into four broad categories: acute radiation nephropathy, chronic radiation nephropathy, benign or malignant hypertension, or symptomless proteinuria. The relationship of the clinical features to dose or dosing schedules is not well defined. Renal dysfunction may present as acute radiation nephropathy, with an abrupt onset after a latent period of 6–12 months following radiation exposure. Chronic radiation nephropathy may present following the acute episode, or may be more indolent, presenting more than 12 months following radiation exposure. Benign or malignant hypertension may occur 18 months to many years...
later. Symptomless, often intermittent proteinuria may be the only sign of radiation-induced kidney toxicity.

The classic clinical features of radiation nephropathy are severe anemia, hypertension, and increasing serum creatinine; proteinuria, microscopic hematuria and edema may also occur. Initially, the anemia presents as normochromic normocytic anemia, but it may present as a hemolytic anemia, which is indicative of thrombomicroangiopathy (TMA).

The presentation of TMA can range from mild subclinical TMA, which would be suspected by thrombocytopenia and fragmented red cells on a blood smear (evidence of endothelial damage) to a fulminant widespread presentation, such as hemolytic uremic syndrome (HUS) or thrombotic thrombocytopenic purpura (TTP). TTP and HUS are considered to be severe manifestations in the spectrum of TMA.

TTP is a syndrome that, classically, has five features: microangiopathic hemolytic anemia (low haptoglobin and fragmented red blood cells), low platelet count, fever, neurological symptoms, and renal failure. TTP is also often associated with an increased serum lactate dehydrogenase (LDH). The renal dysfunction is usually chronic but not always progressive. In addition to radiation exposure, there are several causes of this syndrome, including infection (bacterial and viral), chemotherapy (particularly Mitomycin C), organ transplantation, pregnancy, and collagen vascular disease. These various etiologic factors confound the study of TMA attributable to radiation exposure.

The symptoms of HUS are predominantly renal, with hypertension, edema, and raised serum urea and creatinine levels, in association with microangiopathic hemolytic anemia and thrombocytopenia.

Pathophysiology and Histopathology of Radiation Nephropathy

The kidney is a slowly proliferating tissue and, therefore, radiation toxicity presents as a delayed reaction. Both the capillary endothelium and the tubular epithelium in the kidneys are conditional cell renewal systems, i.e., the cells in these tissues normally do not divide, but have a limited proliferation potential if stimulated, as in response to injury. The tubular epithelial cells appear to be more radiosensitive than epithelial cells from other tissue systems. It is unclear whether the ability of these cells to repair sublethal damage is less than that of other epithelial cells, and whether this contributes to their radiosensitivity.

During the latent interval between radiation exposure and the development of elevated serum creatinine, it is not known what happens pathologically. The pathology findings depend on the time interval between the radiation and the tissue examination. It is known that the pathological findings are similar, whether the irradiation is from single-dose or fractionated photon irradiation, or from fast neutrons.

Tissue damage is seen in both the glomeruli and the tubules. Glomerular capillary endothelial damage is seen within a few weeks of radiation, and then resolves. Mesangial lesions progress and become similar to changes observed in other glomerulopathies. Capillaries in the glomeruli are different from capillaries elsewhere in that their blood pressure is higher. The initial response to radiation is an increase in capillary permeability, more filtrate is extruded from the capillaries, and increased amounts of protein and other high molecular weight blood components escape from the capillaries. These changes are transient, but some extravasated protein remains in the extravascular spaces. This protein gradually becomes insoluble, and contributes to the diffusion barrier that slows the extracellular circulation of oxygen and other essential metabolites, resulting in the changes seen on histological examination. Tubular changes are a late finding, observed after 10 months. Eventually, both glomerular and tubular sclerosis can be seen.

Histopathologically, features of radiation nephropathy are consistent with those of TMA. These findings are nonspecific and include vascular endothelial damage (with endothelial cell dropout, subendothelial widening, and splitting of the capillary basement membrane), mesangial damage or lysis, platelet aggregation in the capillary loops, red-cell fragmentation resulting from microangiopathic hemolysis, thickening of the glomerular arteriolar intimal layer, and atrophic tubules. A history of radiation in a patient with these histological findings would implicate radiation as the cause of the renal failure.

Post-Bone Marrow Transplant Thrombomicroangiopathy (BMT-TMA)

TMA is a condition that has been recognized in patients following BMT. In general, BMT-
TMA occurs within 5–6 months after allogeneic BMT in a setting of other complications, such as cytomegalovirus or fungal infection, graft-versus-host disease (GVHD), or cyclosporin toxicity. However, it may occur in the absence of complications, and may follow autologous BMT. The pretransplant conditioning regime may play a role. The clinical features, the time interval following transplant, and the response to treatment vary widely.

The incidence of BMT-TMA is unclear. Following transplant, the incidence of TMA, including subclinical hemolysis, is estimated to range from 0%–75%. This wide range in reported incidence is likely related to the criteria used for diagnosis. A large Italian study in 1999 reviewing over 4,000 BMT patients reported that severe TMA with all features of TTP probably occurs in less than 1% of patients. The incidence is 0.5% following allogeneic BMT, and 0.13% following autologous BMT. A 1994 review of 207 patients with post-BMT-TMA from 26 publications showed an incidence of TMA of 6.8% following autologous transplant and 13.6% following allogeneic transplant. These patients had multiple known predisposing factors, including GVHD, as well as opportunistic infections such as cytomegalovirus infection, treatment with cyclosporin, or intensive conditioning chemotherapy, such as cyclophosphamide or TBI.

There are three proposed pathological mechanisms for classical TTP. One possible mechanism is a systemic disturbance of endothelial cells that causes a defect in processing of van Willebrand factor multimers, which induce systemic platelet aggregation. An alternative mechanism is a decreased synthesis of prostaglandin I2 (PGI2) by the endothelium, leading to widespread microthrombi in various organs (brain, liver, kidney, and heart). The third proposed mechanism implicates low levels of Protein C as a factor. In classical TTP, plasma exchange with cryosupernatant plasma has reduced the mortality from 90% to 20%. This is not effective in BMT-TTP, suggesting different pathological mechanisms, probably related to the other associated contributing factors.

HUS occurring at 6 months post-transplant has been termed conditioning-associated HUS. Typically, there is minimal systemic involvement and no history of cyclosporin treatment, GVHD, or infection. Post-BMT-HUS is relatively benign, with low mortality. However, residual renal impairment is frequent. Symptoms are delayed to 3–12 months post-BMT. TBI, when given with multiple chemotherapeutic agents, and particularly when unfractionated, is strongly implicated for HUS.

Radionuclide Nephropathy

In addition to the toxicity from radiation exposure following external-beam radiation, radiation nephropathy has recently been observed following targeted radionuclide therapy with small molecules radiolabeled with high doses of beta-emitting radionuclides. There appears to be a threshold radiation-absorbed dose, above which kidney radiation toxicity occurs. This threshold with targeted radionuclide therapy is still under investigation, because of conflicting clinical data and the difficulties in accurately assessing a radiation-absorbed dose from radionuclide therapy.

Even within the setting of internally administered radionuclide therapy, there are differences in delivery. For example, when the radioisotope is bound to the kidney, it will decay at the rate of physical decay, compared to when the radioisotope passes through the kidneys and the dose rate decreases more rapidly, or there may be a combination of these mechanisms. Another difference in delivery of various targeted radiotherapeutics is whether there is a regional deposition in the kidney tissue, or whether there is reabsorption by way of the proximal tubules and, therefore, a longer residence time in the cortex from metabolism, as is the case with small proteins, such as radiolabeled antibody fragments or peptides.

Although the kidney is a large organ, with mass and depth information easily obtainable, the complex physiology and anatomy introduce difficulties in estimating the radiation-absorbed dose to the kidney using a macroscopic approach with photon-counting techniques. For radionuclides that are retained or localized in parts of the kidneys, there will be different residence times in the different kidney regions, as well as different S values to be considered. A MIRD kidney model with regional S values for the kidney (separate cortex and medulla S values) has been published to take these distributions into account for kidney dosimetry, if details of the regional localization are known.

The effect of the continuously decreasing dose rate from targeted radionuclides therapy may be unlike the delivery at a constant dose rate over a short period of time, as is the case with external-
For radionuclides that pass directly through the kidneys into the urine, with no retention in any region of the kidney, the dose–rate effect may be an important factor to consider. This has not generally been considered for internal dosimetry. With the increased use of targeted radionuclide therapy by the administration of high dosages of radionuclides linked to small molecules, the possible impact of the dose–rate effect must be evaluated. The assumptions of tissue repair times and the alpha/beta ratios used for the linear quadratic model approach to assess dose–rate effects, discussed in the paper by Dale in this issue (pp. 363–370) and elsewhere, are based on preclinical or in vitro assessments of tissue repair in normal tissue in mice. These may not be valid for patients who have been exposed previously to chemotherapy agents or have disease that may impact their kidneys. Thus, assumptions used to derive the biological effective dose from dose–rate effects may not be completely valid and will require further investigation.

CONCLUSIONS

The kidneys are said to have memory for prior damage, and may respond differently to radiation following a prior insult, such as nephrotoxic drugs or underlying kidney disease. This should be considered as a functional factor for kidney-dose estimates, as would be the case for the bone marrow dose for patients with prior myelosuppressive therapy, and who, therefore, are more susceptible to the effects of radiation. Such susceptibility must be taken into account, and careful dose escalation studies should be carried out to assess the response of the kidneys to small-molecule-targeted radiotherapeutics in development.

REFERENCES