Precautions Against Thrombotic Microangiopathy after radioligand therapy – Literature Overview

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"Thrombotic microangiopathy (TMA) is rare and its cancer-related subset even more so. TMA triggered by drugs is the most common within this group, including classic chemotherapy and the latest targeted therapies. The neoplastic disease itself and hematopoietic stem-cell transplantation could also be potential triggers."[1]

"Drug-induced nephrotoxicity tends to occur more frequently in certain patients and in specific clinical situations. Therefore, successful prevention requires knowledge of patient-related risk factors, drug-related risk factors, and pre-emptive measures, coupled with vigilance and early intervention."[2]

Types of TMA[3]

The mechanisms of action in TMA differ among thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), and atypical hemolytic uremic syndrome (aHUS):

Thrombotic Thrombocytopenic Purpura (TTP) is primarily caused by a deficiency of the enzyme ADAMTS13, which is responsible for cleaving large von Willebrand factor (vWF) multimers. When ADAMTS13 is deficient or inhibited, these large multimers promote excessive platelet aggregation, leading to microthrombi formation, hemolytic anemia, and thrombocytopenia. Neurological symptoms and renal involvement are common due to microvascular occlusion in various organs.[4] [5]

Hemolytic Uremic Syndrome (HUS) is often associated with infections, particularly those caused by Shiga toxin-producing E. coli (STEC). The toxin damages endothelial cells in the kidneys, leading to platelet activation and the formation of microthrombi. HUS is characterized by a triad of symptoms: microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury. Unlike TTP, neurological symptoms are less prominent.[4] [6]

Atypical Hemolytic Uremic Syndrome (aHUS) is typically due to dysregulation of the complement system, leading to uncontrolled complement activation and subsequent endothelial injury. This condition can be triggered by infections, medications, or genetic factors. The resulting endothelial damage leads to similar outcomes as TTP and HUS, including microthrombi formation and renal impairment.[5] [6]

In summary, while all three conditions involve endothelial damage and microthrombi formation, TTP is linked to vWF dysregulation, HUS often follows infections with toxins, and aHUS is primarily driven by complement dysregulation.

Pre-emptive measures will presumably depend on what type of TMA can be expected. It seems like radioligand therapy (RLT) can trigger any type of TMA (except for classical HUS), because it may exacerbate an existing condition caused by either previous treatments or cancer itself.

[1] Thrombotic microangiopathy in oncology – a review – Elsevier
[2] Drug-Induced Nephrotoxicity – American Family Physician Journal
[3] Thrombotic microangiopathy in oncology – a review – Elsevier
[4] HUS AND TTP – Pediatr.Clin.NorthAm
[5] Is it aHUS? Perhaps it's TTP, STEC-HUS, or Another TMA
[6] Cancer-associated thrombotic microangiopathy - ecancer

Pre-Therapy Assessment and Risk Stratification

Patients with **pre-existing kidney impairment, certain underlying conditions** or **pre-treatments** may be at higher risk of TMA.

- **Underlying conditions**: hypertension, diabetes, pre-existing chronic kidney disease
- **Cancer stage**: bone marrow involvement[6] "Distinguishing cancer-related TMA as a consequence of cancer itself from cases of drug-induced TMA can be challenging. Metastatic disease is more common in cancer-related TMA."[7]
- **Pre-treatments**[2]:
  - quinine
  - immunosuppressive agents (calcineurin inhibitors: ciclosporin and tacrolimus Sirolimus IFN-α, IFN-β)
  - VEGF inhibitors (bevacizumab, sunitinib)
  - Cardiovascular agents (Clopidogrel (Plavix), ticlopidine (Ticlid))
  - chemotherapeutic agents (gemcitabine, mitomycin, 5-fluorouracil, bleomycin, cisplatin, cytosine arabinoside, daunomycin, deoxycoformycin, estramustine, and methyl-CCNU)
  - recreational drugs (cocaine)
  - ticlopidine (ADAMTS13 autoantibody)

Dose Modification and Fractionation

- **Lower dosing or adjusted protocols**: Radioligand doses may be adjusted, especially in patients at risk of renal damage. *(guidelines of European Association of Nuclear Medicine (EANM), American Society of Clinical Oncology (ASCO), National Comprehensive Cancer Network (NCCN))*
- **Fractionated dosing**: Delivering smaller, more frequent doses instead of a single high dose may help reduce kidney damage and prevent the formation of microthrombi in renal vessels. A 2012 study published in The Journal of Nuclear Medicine explored fractionated PRRT dosing to limit radiation exposure to the kidneys and found that dividing the doses allowed for a significant reduction in renal toxicity, without compromising the therapeutic efficacy.[8]

Precautions

Avoid nephrotoxic medications: Patients undergoing RLT should avoid drugs that can further stress the kidneys, such as nonsteroidal anti-inflammatory drugs (NSAIDs) or certain antibiotics (e.g., aminoglycosides).

Preventive measures

Hydration

Adequate hydration before, during, and after therapy

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[7] Eculizumab in chemotherapy-induced thrombotic microangiopathy - Clinical Nephrology. Case Studies
[8] Renal Toxicity of Radiolabeled Peptides and Antibody Fragments: Mechanisms, Impact on Radionuclide Therapy, and Strategies for Prevention - JNM

- Intravenous (IV) fluids
- Diuretics (if appropriate)

Use of Renal Protective Agents

Antioxidants

RLT can generate **reactive oxygen species** (ROS) or free radicals, which cause oxidative stress, damage the endothelial cells lining the blood vessels (including those in the kidneys), and contribute to the development of TMA. Antioxidants neutralize these free radicals, potentially reducing cellular injury. There is some evidence suggesting that antioxidants such as vitamin E, vitamin C, or glutathione could protect against radiation-induced oxidative stress.

Common Antioxidants and Their Roles

	Benefits
Vitamin E[9] **(Tocopherol)**	Vitamin E supplementation can reduce radiation-induced oxidative damage, though its specific impact on preventing TMA during RLT is not fully established. However, it may help protect kidney tissue from the harmful effects of radiation.
Vitamin C[10] **(Ascorbic Acid)**	Vitamin C can be used as a protective agent against radiation-induced tissue damage. In combination with other antioxidants, it may enhance the body's overall ability to fight off oxidative damage in the kidneys during RLT.
Glutathione[9]	Glutathione is often used in medical settings to reduce radiation toxicity. Its role in reducing oxidative damage in the kidneys might help mitigate TMA risk by supporting cellular repair and preventing endothelial damage.
N-acetylcysteine (NAC)[11]	NAC has been used in various clinical settings to protect against kidney damage, such as in cases of contrast-induced nephropathy or acute kidney injury. It may offer protective effects against radiation-induced kidney damage by enhancing glutathione levels, potentially reducing the risk of TMA by preserving kidney function and protecting endothelial cells.
Selenium[9]	Selenium supplementation may help mitigate the effects of radiation on the kidneys by supporting antioxidant activity and protecting cells from oxidative damage.
Coenzyme Q10 (CoQ10)[12]	A study in rats suggests CoQ10 might reduce radiation-induced damage in healthy tissues, including kidneys.
Alpha-Lipoic Acid (ALA)[13]	ALA can protect endothelial cells and reduce damage to tissues exposed to radiation. Its kidney-protective effects in cases of radiation-induced damage have been suggested in some studies.
Antioxidant proteins such as SOD[14]	**Superoxide dismutase (SOD)** antioxidant enzyme converts harmful superoxide radicals into less toxic molecules like hydrogen peroxide. Effectiveness as an oral supplement is limited due to poor absorption.

[9] Oxidant mechanisms in toxic acute renal failure - Drug Metabolism Reviews
[10] Protective Role for Antioxidants in Acute Kidney Disease - Nutrients
[11] N-Acetylcysteine Alleviates the Progression of Chronic Kidney Disease: A Three-Year Cohort Study
[12] Amelioration of Radiation Enteropathy by Dietary Supplementation With Reduced Coenzyme Q10 – Adv Radiat Oncol
[13] Renal-Protective Roles of Lipoic Acid in Kidney Disease - Nutrients
[14] Catalytic Antioxidants in the Kidney - Antioxidants

Catalase[14]	**Catalase** breaks down hydrogen peroxide, a harmful byproduct of oxidative stress, into water and oxygen. Effectiveness as an oral supplement is limited due to poor stability and absorption.
GPx[14]	**Glutathione peroxidase (GPx)** reduces hydrogen peroxide and lipid peroxides, using glutathione (GSH) as a cofactor. It helps maintain cellular integrity and prevents damage associated with conditions like nephrotoxicity. GPx is not typically available as a direct supplement, but its function can be supported by increasing levels of **selenium** (an essential cofactor) and **glutathione**.
Proteins that sequester metals (ferritin, metallothionein[15]**)**	**Ferritin** captures free iron. Iron supplements can indirectly increase ferritin levels. **Metallothionein** binds to and regulates essential metals, like zinc and copper, and detoxifies heavy metals such as cadmium and mercury. In the kidneys, it buffers metal toxicity and reduces oxidative stress, as it scavenges free radicals generated by metal-induced damage. It also helps in the repair and regeneration of kidney tissues after injury. Metallothionein is not available as a direct supplement, but certain **nutrients like zinc** can upregulate its expression.
(HO-1)[16]	**Heme oxygenase-1 (HO-1)** enzyme degrades heme into three products: **biliverdin**, **iron**, and **carbon monoxide**. In the kidneys, HO-1 plays a protective role by breaking down excess heme, which can be toxic and promote oxidative stress. The byproducts of heme degradation, especially biliverdin (which is further converted to bilirubin), have antioxidant and anti-inflammatory properties, helping to protect kidney cells from oxidative damage and inflammation. HO-1 is not available as a supplement, but its expression can be induced by certain **antioxidants** (like curcumin).

ACE inhibitors or ARBs[17]:

In some cases, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs or sartans) may help protect the kidneys by lowering blood pressure and reducing stress on the renal blood vessels.

Sartans are commonly used to treat high blood pressure, heart failure, and kidney protection in diabetic patients. They work by blocking the effects of angiotensin II, a hormone that causes blood vessels to constrict, leading to lower blood pressure and reduced strain on the heart and kidneys. Their benefits in reducing inflammation, protecting endothelial cells, lowering blood pressure, and preventing proteinuria may help reduce the risk of radiation-induced microvascular injury, which could lead to TMA, specifically aHUS.

Renal Protection

Reduction of Glomerular Pressure: Sartans help lower blood pressure in the kidneys by dilating blood vessels, reducing glomerular pressure, and decreasing proteinuria (protein leakage into the urine). This is particularly beneficial in preventing or minimizing kidney damage that can lead to TMA.

[15] The Role of Metallothionein in Oxidative Stress – Int J Mol Sci
[16] Heme Oxygenase-1 in Kidney Health and Disease – Antioxid Redox Signal
[17] Angiotensin II Blockade and Renal Protection – Curr. Pharm. Des

Protection of Endothelial Cells: Angiotensin II is also involved in promoting inflammation and oxidative stress in blood vessels, including the microvasculature of the kidneys. By blocking this hormone, sartans may help protect the endothelial cells that line the small blood vessels in the kidneys, potentially reducing the risk of TMA.

Anti-Inflammatory and Anti-Fibrotic Effects

Reduction of Inflammation: TMA involves inflammation and damage to the endothelial lining of small blood vessels, including in the kidneys. Sartans have been shown to have anti-inflammatory effects, reducing the likelihood of endothelial injury and subsequent microthrombi formation, a hallmark of TMA.

Prevention of Fibrosis: Chronic inflammation and endothelial damage can lead to scarring (fibrosis) in the kidneys, worsening renal function. Sartans help prevent fibrosis by inhibiting the angiotensin II pathway, which can contribute to long-term kidney protection.

Blood Pressure Control

Lowering Blood Pressure: High blood pressure can exacerbate kidney damage, increasing the risk of developing TMA. Sartans effectively lower blood pressure, which reduces the strain on the kidneys and helps protect the microvasculature from damage.

Reduced Risk of Renal Hypertension: Renal hypertension (high blood pressure originating from the kidneys) can worsen kidney damage and increase the risk of TMA. Sartans help manage this by keeping blood pressure under control, which is particularly important in patients undergoing RLT who may already have pre-existing kidney stress.

Prevention of Proteinuria

Proteinuria is often a sign of kidney damage, and it can worsen the progression of kidney disease. Sartans are known to reduce proteinuria by lowering glomerular filtration pressure and protecting the kidney's filtering units. This can indirectly help prevent the kidney damage that may lead to TMA, especially in patients with pre-existing kidney conditions.

Plasma Exchange & Corticosteroids[18] [19]

For those with a history of **TTP**, early plasma exchange and corticosteroids treatment can reduce the risk of TMA recurrence. But it plays no role in Shiga toxin-mediated TMA (HUS).[20]

“Evidence from a retrospective study suggests that relapsed or **refractory TTP** can be managed successfully by increasing the intensity or frequency of plasma exchanges and adding or increasing doses of immunosuppressant therapy, including corticosteroids.”[19]

Eculizumab[7]

In some cases, the use of complement inhibitors like **eculizumab,** a monoclonal antibody against complement factor C5, can be considered, especially if **TMA is mediated by complement system activation**, which is a potential pathway involved in kidney damage during RLT. Successful treatment described in case of gemcitabine-induced hemolytic uremic

[18] Evidences of histologic thrombotic microangiopathy and the impact in renal outcomes of patients with IgA nephropathy – PLoS One
[19] Thrombotic microangiopathies: a general approach to diagnosis and management – Canadian Medical Assoc. J
[20] Prostate cancer-associated thrombotic microangiopathy: A case report and review of the literature – J Clin. Nephr.

syndrome (**GiHUS**).[21] "Those receiving treatment with eculizumab are particularly vulnerable to infection with encapsulated organisms as host defence is dependent on the complement membrane attack complex. Therefore, vaccination for *Neisseria meningitides* "at least two weeks prior to treatment"[6] is required as well as prophylactic antibiotics for all those taking eculizumab."[22]

Admittedly, all cases described above refer to therapy rather than prophylactic use. There are several mentions of using eculizumab pre-emptively before renal transplantation.[19] [23]

Ravulizumab

"Ravulizumab was engineered from eculizumab for the treatment of patients with aHUS and targets the same epitope in C5. A histidine switch was performed in the complementarity-determining regions of eculizumab to preserve binding to C5 in serum but to allow dissociation of C5 from ravulizumab in the acidified endosome. Additionally amino acid alterations to the Fc region of eculizumab resulted in increased efficiency of neonatal Fc receptor-mediated recycling. This resulted in ravulizumab having an increased half-life of ~52 days compared to ~11 days with eculizumab and therefore, up to an 8-week dosing interval with ravulizumab versus 2 weekly with eculizumab."[22]

Rituximab

There are several papers about the prophylactic use of rituximab, the monoclonal antibody to CD20 on the surface of B-cells, both about its pre-emptive use meant to prevent a relapse of acquired TTP, for example:

1. Rituximab for thrombotic thrombocytopenic purpura: benefit of early administration during acute episodes and use of prophylaxis to prevent relapse
2. Pre-emptive rituximab infusions after remission efficiently prevent relapses in acquired thrombotic thrombocytopenic purpura

[21] Eculizumab therapy for gemcitabine induced hemolytic uremic syndrome: case series and concise review - J Gastrointest Oncol.
[22] Diagnosis and treatment of thrombotic microangiopathy - Int J Lab Hematol.
[23] Thrombotic Microangiopathy After Kidney Transplantation: An Underdiagnosed and Potentially Reversible Entity - Frontiers in Medicine

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