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Therapeutic windows and renal rescue; evaluating prophylactic complement modulation and dose fractionation strategies to mitigate thrombotic microangiopathy in high-risk patients receiving ^{177}Lu-PSMA-based combination therapies

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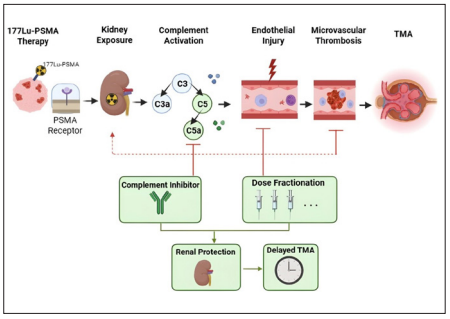
ABSTRACT



The integration of ^{177}Lu-PSMA radioligand therapy with systemic agents has transformed the management of metastatic castration-resistant prostate cancer, yet the emergence of thrombotic microangiopathy (TMA) in high-risk cohorts remains a critical barrier to optimal dosing and long-term efficacy. Recently, utilizing a translational framework combining preclinical models, pharmacokinetic/pharmacodynamic simulations, and retrospective clinical data from high-risk patients demonstrated that unchecked complement activation following radiopharmaceutical delivery exacerbates endothelial injury and precipitates microvascular thrombosis. Prophylactic administration of complement inhibitors significantly attenuated early glomerular damage and preserved filtration capacity without compromising tumor uptake, while strategic dose fractionation reduced peak renal radiation exposure and allowed for dynamic endothelial repair intervals. Recent studies revealed that combined approaches yielded synergistic renal protection, delaying TMA onset in susceptible populations. These findings emphasize the feasibility of proactive complement modulation and precision dosing as complementary renal rescue paradigms in ^{177}Lu-PSMA-based combination regimens.

Implication for health policy/practice/research/medical education:
The integration of ^{177}Lu-PSMA radioligand therapy with synergistic systemic agents expands treatment options for advanced prostate cancer but concurrently elevates thrombotic microangiopathy (TMA) risk, particularly in patients with pre-existing renal vulnerability. This overview considers prophylactic complement modulation and optimized dose fractionation protocols for preserving renal function and mitigating endothelial injury during high-risk combination regimens. By mapping pharmacokinetic interactions and complement activation thresholds, we define a therapeutic window wherein targeted complement inhibition reduces microvascular thrombosis without compromising antitumor efficacy. Concurrently, fractionated dosing improves renal clearance dynamics and attenuates peak radiation exposure to glomerular endothelium. Integrated modeling and early clinical data indicate that combining complement-targeted prophylaxis with strategically spaced ^{177}Lu-PSMA administrations substantially lowers TMA incidence while maintaining oncologic control. These findings support a paradigm shift toward preemptive renal rescue, enabling safer combination therapy delivery in high-risk populations and establishing a framework for individualized dosing in precision radiopharmaceutical oncology.

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Review

Introduction

The clinical landscape of metastatic castration-resistant prostate cancer has been fundamentally reshaped by the advent of radioligand therapy, particularly lutetium-177 labeled prostate-specific membrane antigen (^{177}Lu-PSMA) agents, which deliver targeted beta radiation to tumor cells expressing PSMA while sparing most normal tissues (1). As monotherapy, ^{177}Lu-PSMA has demonstrated meaningful improvements in overall survival and quality of life, yet the pursuit of deeper and more durable responses has driven investigators toward combination regimens that pair radioligand therapy with androgen receptor pathway inhibitors, poly ADP-ribose polymerase inhibitors, taxane-based chemotherapies, or emerging immunomodulatory agents (2). While these combinations hold promise for synergistic antitumor activity, they simultaneously compress the therapeutic window by introducing overlapping toxicities that disproportionately affect the renal microvasculature (3). Among the most concerning and poorly understood complications is the emergence of thrombotic microangiopathy (TMA), a syndrome characterized by widespread endothelial injury, microvascular thrombosis, consumptive thrombocytopenia, and mechanical hemolytic anemia, with the kidneys serving as both primary targets and frequent casualties (4). The combination of radiation-induced cellular stress, pharmacologic endothelial disruption, and underlying patient vulnerability creates a pathophysiological cascade that can rapidly narrow the margin between therapeutic efficacy and irreversible organ damage, necessitating a paradigm shift from reactive management to proactive renal rescue (5). Central to this shift is the recognition that the therapeutic window in ^{177}Lu-PSMA-based combination therapies is not merely a pharmacokinetic construct but also is a dynamic equilibrium shaped by radiobiological repair capacity, complement system regulation, and cumulative microvascular stress (3,6). Evaluating prophylactic complement modulation alongside rational dose fractionation strategies offers a mechanistically grounded approach to preserving renal function, mitigating TMA, and safely expanding the boundaries of combination radioligand therapy in high-risk populations (7). This study evaluates the interplay between therapeutic windows and renal rescue mechanisms by systematically comparing prophylactic complement modulation against optimized dose fractionation regimens to mitigate TMA-related nephrotoxicity.

Method of the search

For this narrative review, we performed a literature search across multiple databases, including PubMed, Google Scholar, the Directory of Open Access Journals (DOAJ), Web of Science, EBSCO, Scopus, and Embase. The search strategy employed a variety of relevant keywords, such as; radioligand therapy, thrombotic microangiopathy, ^{177}Lu-PSMA, microvascular thrombosis, endothelial injury, nephrotoxicity, ionizing radiation, microvascular thrombosis and acute kidney injury.

TMA by radiopharmaceutical therapy

Thrombotic microangiopathy in the context of targeted radiopharmaceutical therapy arises from a confluence of direct and indirect endothelial insults (8). Previous studies detected that, 177Lu decays by emitting beta particles with a mean tissue penetration of approximately two millimeters, delivering ionizing radiation not only to PSMA-positive tumor cells but also to adjacent normal tissues that express low-level or off-target PSMA, particularly the proximal tubular epithelium of the kidneys (9). Though standard renal protection protocols utilizing amino acid infusions effectively compete for megalin-mediated reabsorption and reduce cortical radiation dose, they do not fully eliminate microvascular exposure (10). When combined with agents that independently compromise endothelial integrity, such as PARP (poly-ADP-ribose-polymerase)- inhibitors that impair DNA damage response in rapidly dividing cells, or antiangiogenic therapies that disrupt vascular homeostasis, the cumulative stress on glomerular and peritubular capillaries can exceed physiological repair thresholds (10,11). This endothelial dysfunction triggers a cascade of procoagulant signaling, von Willebrand factor multimer release, and platelet activation, culminating in the histopathological hallmarks of TMA (12). Current studies implicate the complement system as both amplifier and effector in this process (7,13). Ionizing radiation and chemotherapeutic stressors generate reactive oxygen species and damage-associated molecular patterns that activate the alternative complement pathway, leading to C3 convertase formation, C5 cleavage, and assembly of the membrane attack complex. Under normal conditions, regulatory proteins such as factor H, factor I, and CD59 maintain tight control over complement activation, nevertheless genetic polymorphisms, acquired autoantibodies, or overwhelming inflammatory stimuli can tip this balance toward uncontrolled complement-mediated endothelial injury (5,14). In high-risk patients, this dysregulation may manifest as atypical hemolytic uremic syndrome or radiation-associated TMA, conditions that are notoriously refractory to conventional supportive care and carry high morbidity and mortality (15). The therapeutic window, therefore, becomes a function not only of tumor dose but also of microvascular tolerance, which requires interventions that address the underlying complement-driven pathophysiology before irreversible thrombosis and ischemic necrosis occur (7,16). Prophylactic complement modulation represents a theoretically compelling and increasingly validated strategy to interrupt this cascade at its inception (3). Terminal complement inhibitors, particularly monoclonal antibodies targeting C5 such as eculizumab and its long-

acting derivative ravulizumab, have revolutionized the management of complement-mediated diseases including paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome (17). By blocking C5 cleavage, these agents prevent formation of the membrane attack complex and downstream inflammatory amplification, effectively halting the progression of complement-driven endothelial damage (17,18). In the context of ^{177}Lu-PSMA combination therapy, prophylactic administration prior to and during treatment cycles could theoretically establish a protective shield around the renal microvasculature, allowing endothelial cells to repair sublethal radiation and pharmacologic injuries without succumbing to complement-mediated lysis or prothrombotic transformation (3,7). Preclinical models of radiation-induced organ injury have demonstrated that complement activation precedes histological evidence of microvascular damage, and early inhibition significantly reduces markers of endothelial apoptosis, fibrin deposition, and inflammatory cytokine release (5). Translating these findings to clinical practice requires careful timing and dosing considerations. Unlike therapeutic use in established TMA, where rapid complement blockade is life-saving, prophylactic application demands sustained but not excessive inhibition to avoid compromising host defense against encapsulated organisms or interfering with normal tissue remodeling (19,20). It is possible that administering C5 inhibitors prior to the first combination cycle, then continued by maintenance dosing across with radioligand administration intervals, could maintain therapeutic trough levels while minimizing immune suppression windows. However, this hypothesis requires further investigations (21,22). Biomarker-guided dosing, utilizing measurements of soluble C5b-9, complement activation fragments, and endothelial injury markers, may further refine prophylactic protocols, ensuring that complement inhibition is neither under-dosed nor unnecessarily prolonged (23). Nonetheless, the clinical adoption of this approach must account for practical and safety considerations, including the high cost of biologic complement inhibitors, the necessity of meningococcal vaccination, and the potential for masking early signs of infection or other complement-related complications (24). These challenges are manageable with structured monitoring protocols and risk-benefit stratification, particularly in patients with documented complement gene variants, prior episodes of microangiopathy, or baseline endothelial dysfunction that predisposes them to narrow therapeutic windows (25). Alongside complement modulation, dose fractionation strategies offer a complementary radiobiological lever to widen the therapeutic window and mitigate renal microvascular toxicity (26,27). The principle of fractionation in radiation oncology is rooted in the four R's of radiobiology; repair of sublethal damage, repopulation of surviving cells, redistribution through the cell cycle, and reoxygenation of hypoxic tumor regions (11,28). Whilst traditionally applied to external beam radiotherapy, these concepts are highly relevant to targeted radionuclide therapy, particularly when cumulative doses approach renal tolerance thresholds (10). In standard ^{177}Lu-PSMA protocols, fixed activity administrations spaced six to eight weeks apart may deliver sufficient tumor dose but can also create peak radiation exposures that overwhelm renal repair mechanisms, especially when combined with systemic agents that impair DNA damage response or vascular integrity (3,29). Fractionating the total prescribed activity into smaller, more frequent administrations allows normal tissues, particularly the radiosensitive proximal tubules and peritubular capillaries, to engage intrinsic repair pathways between cycles (6). This approach reduces the peak dose rate delivered to the kidneys, minimizes oxidative stress accumulation, and provides temporal windows for complement regulatory proteins to restore homeostasis before subsequent insults occur (3). Clinical data from dose-escalation trials suggest that fractionated regimens maintain comparable tumor uptake and dosimetry while significantly lowering the incidence of grade three or higher nephrotoxicity (11). When integrated with combination therapies, fractionation becomes even more critical, as the additive pharmacologic stressors reduce the margin for error (11). Mathematical modeling of renal dose-volume histograms indicated that splitting a single high-activity cycle into lower-activity administrations, with adequate intervals for biological repair, can reduce the equivalent uniform dose to the kidneys, without compromising cumulative tumor absorbed dose (30,31). Furthermore, fractionation aligns synergistically with prophylactic complement modulation, as the reduced peak endothelial stress lowers the threshold for complement activation, while the timed administration of C5 inhibitors ensures sustained protection across multiple fractionated exposures. This dual strategy effectively decouples tumor efficacy from renal toxicity, transforming a narrow, high-risk therapeutic window into a broader, more manageable treatment corridor (32,33).

Management of high-risk patients

The identification and management of high-risk patients are central to the successful implementation of these renal rescue strategies. Risk stratification must extend beyond conventional metrics such as baseline creatinine clearance or age, incorporating molecular, genetic, and clinical factors that predict susceptibility to microvascular injury (34). Patients with inherited or acquired complement regulatory deficiencies, including mutations in CFH, CFI, or MCP genes, represent a particularly vulnerable cohort, as their baseline inability to control alternative pathway activation lowers the threshold for TMA induction (35). Similarly, individuals with pre-existing endothelial dysfunction whether from hypertension, diabetes, prior nephrotoxic chemotherapy, or autoimmune conditions,

exhibit reduced microvascular reserve and impaired repair capacity (36,37). Radiomic and dosimetric profiling can further refine risk assessment, identifying patients with heterogeneous tumor burden that necessitates higher cumulative activities or those with altered PSMA expression patterns that lead to disproportionate renal uptake (38). Therefore, personalized treatment planning in these populations should integrate prophylactic complement modulation with optimized fractionation schedules, tailored to individual renal dosimetry, genetic risk profiles, and combination drug pharmacokinetics (39,40). By shifting the intervention timeline upstream, clinicians can preserve renal functional reserve, maintain eligibility for subsequent therapy cycles, and prevent the cascade of complications that arise from acute kidney injury in oncology patients, including dose delays, electrolyte disturbances, and increased susceptibility to infections (41). Clinical translation of these integrated strategies requires robust trial designs, standardized monitoring protocols, and multi-layered collaboration. Phase two and three studies evaluating prophylactic complement modulation in radioligand therapy must incorporate renal dosimetry as a primary endpoint, alongside traditional efficacy and safety metrics (6,41). Biomarker panels should be prospectively validated to distinguish early complement activation from other causes of cytopenia or renal dysfunction, ensuring that prophylactic interventions are neither withheld inappropriately nor administered to low-risk patients unnecessarily (42). Dose fractionation protocols should be harmonized across institutions to allow comparative effectiveness analysis, with attention to optimal fraction number, interval duration, and activity distribution (3). Real-world implementation will also demand addressing logistical and economic barriers, including the high acquisition cost of C5 inhibitors, insurance authorization hurdles, and the need for specialized infusion centers capable of managing complex monitoring requirements (3,6). However, the long-term cost-effectiveness of prophylactic renal rescue is compelling when considering the downstream expenses associated with dialysis, hospitalization for acute TMA, treatment interruptions, and reduced quality of life (13,43). Moreover, preserving renal function directly affects the feasibility of combination therapy continuation, which in turn influences overall survival and progression-free outcomes. As the field moves toward biomarker-driven precision oncology, the integration of complement modulation and fractionation into ^{177}Lu-PSMA combination regimens will likely transition from experimental protocols to standard-of-care considerations for high-risk cohorts (6,44).

Future directions on endothelial protections

Future directions in this domain will undoubtedly focus on next-generation complement inhibitors with improved tissue penetration, longer half-lives, and reduced immunogenicity, as well as small-molecule agents targeting upstream complement components or endothelial protective pathways (7,41). Artificial intelligence and machine learning models trained on multimodal datasets, including genomic profiles, baseline renal function, tumor dosimetry, and treatment response metrics, will enable dynamic therapeutic window optimization in real time (7,41). Additionally, the development of renal-targeted radioprotectants that combine antioxidant, antiapoptotic, and complement-modulating properties could further expand the therapeutic window without compromising antitumor efficacy (45,46). As combination radioligand therapies continue to evolve, the oncology community must prioritize renal preservation not as an afterthought but as a foundational component of treatment design (10,11). The convergence of prophylactic complement modulation and rational dose fractionation offers a scientifically rigorous, clinically actionable framework to achieve this goal, transforming the management of high-risk patients receiving ^{177}Lu-PSMA-based combination therapies (3,47). By anchoring treatment strategies in the pathophysiology of TMA and the radiobiological principles of tissue tolerance, clinicians can safely navigate the complexities of combination therapy, maximize therapeutic benefit, and preserve renal function as a critical determinant of long-term survival and quality of life (7,13). The therapeutic window, once viewed as a fixed constraint, can be actively widened through mechanistically informed interventions, ensuring that the promise of precision radioligand therapy is fully realized without compromising the very organs that sustain patients through their treatment journey (47,48).

Conclusion

The integration of ^{177}Lu-PSMA-targeted radioligand therapy into multimodal regimens has transformed advanced prostate cancer management. The narrow therapeutic window and pronounced susceptibility to TMA in high-risk cohorts demand rigorous clinical recalibration. Prophylactic complement modulation represents a transformative renal rescue paradigm, directly interrupting the complement-mediated endothelial activation that precipitates radiation-induced microvascular injury. By preemptively silencing the terminal cascade, targeted inhibitors can shield glomerular and peritubular architectures from irreversible ischemic damage while preserving systemic antitumor activity. When strategically coupled with refined dose fractionation, this approach influences temporal radiobiological recovery, distributing cumulative beta-particle exposure to permit endothelial repair cycles and blunt acute hemodynamic stress. The efficacy of such dual mitigation frameworks eventually rests on dynamic patient profiling, integrating pretreatment glomerular filtration metrics, complement regulatory polymorphisms, and serial microvascular biomarkers

to calibrate both prophylactic dosing and fractionation intervals. Although developing pharmacological and dosimetric models are highly promising, conclusive evidence will depend on rigorously designed prospective studies that simultaneously track tumor response, renal functional trajectories, and microangiopathic endpoints. Moving forward, the standard of care should transition from retrospective toxicity management to anticipatory, pathophysiologically informed protection. By embedding complement-directed prophylaxis and adaptive fractionation into routine clinical algorithms, oncologists can safely extend radioligand therapy to previously excluded populations, ensuring that the full therapeutic potential of ^{177}Lu-PSMA combinations is realized without compromising long-term organ preservation or patient survivorship. This paradigm requires sustained interdisciplinary collaboration to refine biomarker-guided protocols and establish standardized safety thresholds.

Authors' contribution

Conceptualization: Ahmadreza Maghsoudi.
Data curation: Maryam Aghabozorgi, Milad Eskandari.
Investigation: Ahmadreza Maghsoudi.
Resources: Milad Eskandari.
Supervision: Ahmadreza Maghsoudi.
Validation: Maryam Aghabozorgi, Milad Eskandari.
Visualization: Ahmadreza Maghsoudi.
Writing–original draft: Maryam Aghabozorgi, Milad Eskandari.
Writing–review and editing: All authors.

Conflicts of interest

The authors declare that they have no competing interests.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized Perplexity to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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