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The Role of Nurses in the Management of Adverse Events in Patients Receiving First-Line Axitinib Plus Immuno-Oncology Agents for Advanced Renal Cell Carcinoma

Sara Parreira[a], Kathleen Burns[b], Nancy Moldawer[c], Nazy Zomordian[d], Nesan Bandali[e], Kiran Virdee[f], Meghara Walsh[g], Daniel Kelly[h], Dharanija Rao[i], Rosemary Teresi[j], Laura S. Wood[k,*]

[a] *CUF Oncology, Lisbon, Portugal*
[b] *Dana-Farber Cancer Institute, Massachusetts*
[c] *Cedars Sinai Medical Center, Samuel Oschin Comprehensive Cancer Institute, California*
[d] *UCLA, Department of Urology, California*
[e] *Sunnybrook Odette Cancer Centre, ON, Canada*
[f] *Memorial Sloan Kettering Cancer Center, New York*
[g] *Dana-Farber Cancers Institute, Massachusetts*
[h] *Cardiff University, Wales, UK*
[i] *Pfizer Inc., NY, USA*
[j] *Pfizer Inc, NY, USA*
[k] *Cleveland Clinic Cancer Center, Cleveland, Ohio (retired)*

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ABSTRACT

Objectives: The recent approval of first-line tyrosine kinase inhibitor plus immuno-oncology agent combination therapy for the treatment of advanced renal cell carcinoma offers substantially improved response rates and survival compared with the previous standard of care. This expansion of treatment options has also led to a greater range and complexity of potential treatment-related adverse events related to overlapping toxicities. The aim of this article is to discuss the management of common treatment-emergent adverse events (AEs) associated with axitinib plus immuno-oncology therapy, highlight the specific roles of oncology nurses in managing these events, and provide AE management resources to aid oncology nurses in their care of patients with advanced renal cell carcinoma.
Data Sources: Author experience, journal articles, and treatment guidelines were used.
Conclusion: The use of oncology nurses and nurse-led innovations to monitor and assess treatments can have a positive impact on the management of AEs in cancer patients by identifying those who are most at risk, providing regular assessment, appropriate patient education, and supporting the monitoring of patient safety.
Implications for Nursing Practice: Skilled oncology nurses should be a key part of a team that addresses the supportive care needs and management of AEs that are associated with novel cancer treatments. Early and ongoing communication between the patient and oncology nurses regarding the development of adverse events is a critical component of maximizing treatment outcomes and quality of life.

Introduction

Cancer care and treatment represent a constantly evolving field, marked by the approval of multiple new agents and their use as monotherapy or in combination. Advanced renal cell carcinoma (aRCC) is one such cancer that has seen a dramatic shift in treatment approach during the past two decades. The approval of the vascular endothelial growth factor receptor (VEGF-R) targeting tyrosine kinase inhibitors (TKIs) sorafenib in 2005 and sunitinib in 2006 marked the introduction of the targeted therapy era in the treatment of aRCC. The US Food and Drug Administration approval of nivolumab plus ipilimumab in 2018, followed by the combination axitinib plus pembrolizumab, among others, in 2019 marked the emergence of immuno-oncology (IO) agents in the front-line treatment of people with aRCC. Existing and emerging first-line regimens now include the TKIs axitinib, cabozantinib, and lenvatinib and the IO agents avelumab, ipilimumab, nivolumab, and pembrolizumab either as

* Address correspondence to.
E-mail address: woodls401@gmail.com (L.S. Wood).

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monotherapy or as combination therapy, resulting in numerous treatment options across multiple lines of therapy.[1,2]

As evidenced by randomized clinical trials[3-8] and emerging real-world data,[9-11] the approval of IO combination regimens in the first-line setting of aRCC has substantially improved response rates and survival compared with the previous TKI monotherapy standard of care. For example, the range of progression-free survival for IO combination regimens in randomized clinical trials was 11.2–23.9 months versus 8.0–12.3 months for TKI monotherapy.[3-7,12]

The availability and efficacy of multiple first- and later-line treatment options for aRCC have also led to a greater range and complexity of potential treatment-related adverse events (TRAEs).[13] The increased use of combination therapies presents further challenges in the management of TRAEs related to overlapping toxicities. Effective management of TRAEs is needed to optimize treatment adherence and duration, and consequently improve clinical outcomes.

Effective cancer care is provided through a multidisciplinary team, with oncology nurses usually acting as the first point of contact for a patient reporting a TRAE and thus playing a key role in TRAE management.[14] Timely interventions, often led by nurses in collaboration with advanced practice colleagues and oncologists, have shown effectiveness across common cancer symptoms, including fatigue, constipation, nausea and vomiting, anxiety, depression, and mood when compared with usual care or attention control.[15]

The role of the nurse in oncology has evolved and expanded over the years from direct patient care to nurse-led clinics, genetic counseling, treatment prescreening and management, and institutional leadership.[16] Nurse-led innovations in patient care (ie, interventions that are primarily provided by nurses) have been shown to have a positive impact through provision of additional support in key areas of unmet need, such as TRAE management, physical and psychosocial well-being, and patient education.[17,18] A survey of healthcare professionals in the United Kingdom reported that an increase in the involvement of nurses in TRAE management would likely improve patient care; however, only approximately half of the nurses surveyed were willing to expand their roles in this area.[19] One possible explanation is that nurses do not believe they have the time or resources to do so. As the role of the oncology nurse expands, time constraints and a continued need for additional education of nurses remain potential barriers to expanding their roles in TRAE management.[19-21] Through collaborative efforts, oncology nurses have formulated immunotherapy management guidelines and recommendations for adverse events (AEs), as well as patient-directed materials to help improve treatment tolerability.[22]

The aims of this article are to discuss the management of common TRAEs associated with axitinib plus IO therapy, to clarify the specific role of oncology nurses in managing these events, and to provide TRAE management resources to aid oncology nurses in their care of patients with aRCC.

Mode of Action and Potential TRAEs

Axitinib exerts an antiangiogenic effect through the selective inhibition of VEGF-R 1–3. Axitinib is approved for the first-line treatment of aRCC when used in combination with avelumab[5,8,23] or pembrolizumab[24,25] and as monotherapy in the second-line treatment.[26] Pembrolizumab and avelumab are anti–programmed cell death protein 1 (PD-1) and anti–programmed cell death ligand 1 (PD-L1) antibodies and will be referred to collectively as IO agents throughout. Pembrolizumab binds to and blocks PD-1 on T cells, triggering T cells to target cancer cells. Avelumab binds to and blocks PD-L1, resulting in T-cell activation against cancer cells. The combination of antiangiogenic TKIs and anti-PD1/PD-L1 antibodies targets two key, nonoverlapping processes used by cancer cells for survival and growth (ie, angiogenesis and immune evasion), leading to substantially improved outcomes compared with TKI monotherapy as previously discussed (Fig 1).

TRAEs with antiangiogenic agents such as axitinib are mediated by a variety of different underlying mechanisms and are generally not immune mediated.[27] In contrast, treatment with IO agents may result in TRAEs predominantly caused by nonspecific activation of the immune system and may affect multiple organ systems. Common (>10%) TRAEs that are overlapping and may be IO or axitinib related include hypothyroidism and hyperthyroidism, rash/inflammatory dermatitis and pruritus, diarrhea, increased alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), nausea, arthralgia, and general disorders such as fatigue.[27] The management of hypothyroidism, hyperthyroidism, rash/inflammatory dermatitis, pruritus, and arthralgia TRAEs is covered in detail in available expert guidelines.[13,28,29] TRAEs that may need specialized management have been identified as diarrhea, hepatic toxicity, fatigue, and cardiovascular AEs.[27] These TRAEs have potential overlap between axitinib and IO agents. The TRAEs focused on herein represent some of those commonly seen by oncology nurses that may also require determination of their etiology to provide the optimal treatment management and significant TRAEs that with proper intervention can be prevented or minimized.

Determining TRAE Etiology

Axitinib has a relatively short half-life in the plasma (2.5–6.1 h after a single 5-mg dose) compared with pembrolizumab (~14–27 days) and avelumab (~6 days).[30,31] This allows for a general strategy that can be applied for many TRAEs as a first step in determining whether an AE is related to axitinib or the IO agent. In the absence of severe symptoms or toxicities that would require withholding both medications (see product's prescribing information), withholding axitinib for 24–48 hours and monitoring the patient should allow for a quick decrease in axitinib plasma concentrations and, if the TRAE is axitinib-related, a relatively quick recovery from the AE. In support of this approach, an analysis of the time to resolution (TTR) after treatment interruption of five of the most common AEs associated with axitinib treatment (diarrhea, fatigue, hypertension, nausea, and hand-foot syndrome) found that TTR was generally shorter for axitinib monotherapy (≤3 days, except for fatigue) compared with axitinib + IO combinations (4–11 days).[32]

Role of Oncology Nurses in Managing TRAEs

Pretreatment

Oncology nurses are typically the healthcare professionals who spend the most time with the patient. In this respect, oncology nurses are fundamental to provide patient support, education, and AE monitoring and management, all of which can contribute to treatment adherence and improved tolerance. This is specifically relevant to agents such as axitinib as it is self-administered twice daily orally, whereas IO agents are generally administered by intravenous infusion every 2–6 weeks in clinic.

Some people are more likely to face the risk of inadequate AE management, for example, those who are elderly, living alone, and/or coping with comorbidities.[33] Patients should ideally have more than one clinic visit prior to initiating therapy. This time is vital to establish a relationship and provide patient education. The educational materials should include the treatment mode of action, expected response to treatment, potential AEs, and how to spot them, who to contact in case an AE develops, and the importance of treatment adherence.[16] This moment of interaction is an opportunity to address common concerns, questions, and expectations; make a review of potential drug–drug interactions; and educate on which foods to avoid, if applicable.[16]

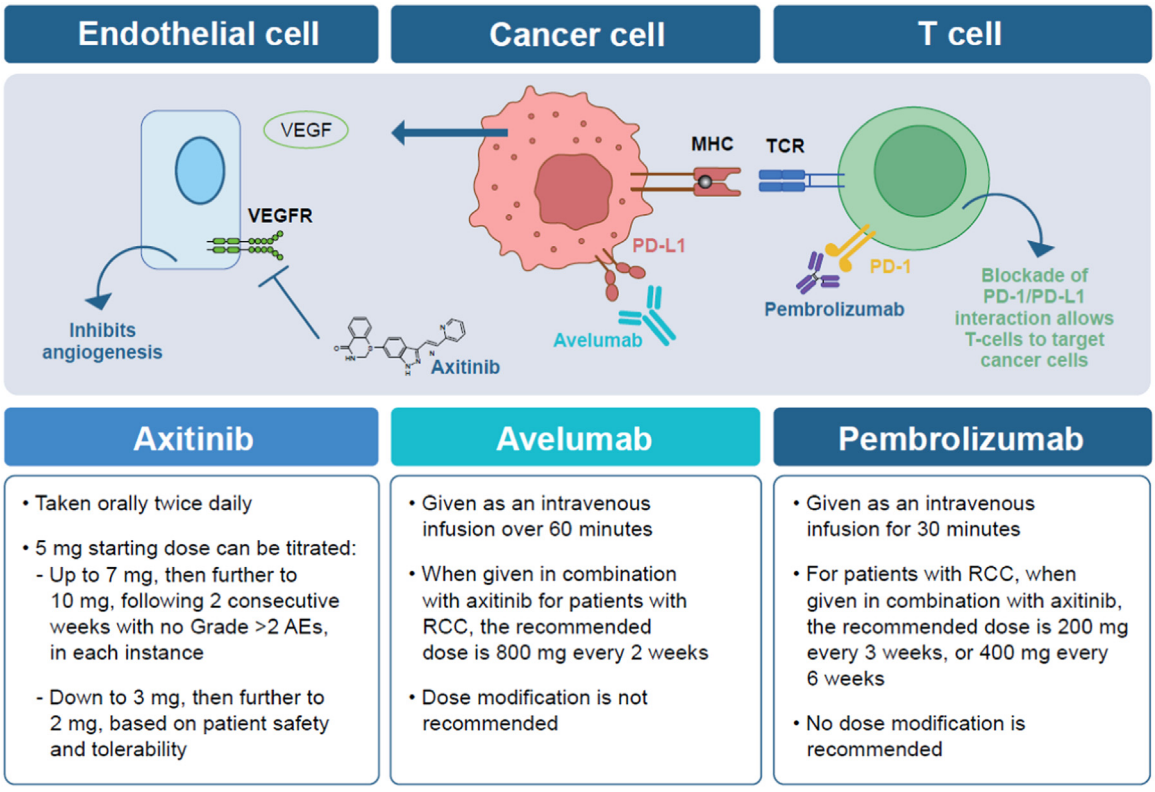

Fig 1. Mechanism of action for the combination of axitinib and immuno-oncology agents in advanced renal cell carcinoma. AE, adverse event; MHC, major histocompatibility complex; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1; RCC, renal cell carcinoma; TCR, T-cell receptor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

Education is essential both for oncology nurses and for patients with this cancer and their caregivers in helping understand how to best care and advocate for themselves through management of potential TRAEs, including when and how to contact their healthcare team.[34] This is especially important during the initial diagnosis and treatment initiation. Education for potential TRAEs often focuses on worst case scenarios, which can seem overwhelming; therefore, effective education, reassurance, and clear direction on what to do if an AE develops are critical and can improve patient anxiety and self-care.[35] Education should also focus on those TRAEs that initially can be self-managed at home and provide guidance on recognizing when symptoms require urgent contact with the healthcare team. Patient education is most effective before treatment initiation, and TRAEs and management strategies are among the most important topics that have been shown to help reduce patient anxiety.[36] It should be emphasized that prompt communication to their healthcare team about any AEs that may arise is essential.[37]

There would likely be value in ensuring patients received a one-sided, quick resource leaflet, or similarly concise information, advising them on the signs of TRAEs to look for. As patients are given a substantial amount of new information when starting treatment, they may feel overwhelmed, so an easy, quick reference sheet with helpful contact numbers could help communicate the key points effectively. An example side effect communication resource is provided in **Supplementary Figure 1**.

During Treatment

After beginning treatment, it is optimal to have patient follow-up visits within 2 weeks for a toxicity review and laboratory tests. Follow-up phone calls or virtual visits can occur in lieu of a clinic visit. Regular scheduled clinic visits with the healthcare team and ensuring time is spent with an oncology nurse may also help identify patients who are potentially nonadherent. For example, a patient who is not demonstrating any side effects might not be dosing axitinib twice a day. This patient could be underdosing and therefore compromising their therapeutic outcome. Regular contact with oncology nurses can also help to identify patients who may be unclear about the treatment plan or regimen and possibly not taking the drug correctly. Frequent communication between oncology nurses and patients, for example, via clinic visits or regular telephone calls, can aid timely reporting of AEs and may lead to prolonged treatment duration.[38] It would be optimal if patients were to have a primary point of contact within the care team to ensure that information is communicated effectively.

The use of a paper or electronic diary that allows patients to record their own symptoms daily may be beneficial in the early identification and management of AEs. A sample patient diary is provided in **Supplementary Table 1**. AEs are commonly reported using the Common Terminology Criteria for Adverse Events (CTCAE) via consultation between the physician and patient. Toxicities such as nausea and diarrhea may be underreported, especially if low grade; therefore, it is important to ask the patient about specific and common TRAEs.[39] A feasibility study of patients in multicenter cancer trials found that patients were willing and able to report symptomatic AEs using an electronic device, and often reported more AEs than investigators.[40] The successful use of such a diary would rely upon consistent adherence by the patient and would be best used as a complement to clinical care and guidance.

Management of Specific TRAEs

Diarrhea

For patients who report diarrhea, oncology nurses will need to gather important information, including when the diarrhea began,

the frequency of bowel movements per day, the consistency, the presence of blood, whether there have been any dietary changes since the diarrhea started, and whether the patient is taking any medication for it. Monitoring bowels before the initiation of treatment is important to attempt to break down the barriers of potential embarrassment and underreporting of diarrhea. This approach also allows an accurate measure of baseline bowel function for comparison upon treatment initiation. Additional information that will need to be gathered during a clinical visit may include blood pressure and laboratory testing for blood urea nitrogen, creatinine, AST, ALT, and total bilirubin.[41]

Oncology nurses can provide supportive care measures to help manage diarrhea by encouraging patients to maintain hydration and dietary measures (incorporate the BRAT [bananas, rice, applesauce, toast] diet, eat frequent small meals, avoid alcohol and caffeine, avoid fatty and spicy foods), keep a stool diary, advise patients on the best way to clean and dry the rectal area, and advise on over-the-counter and prescription antidiarrheal agents.[42] Management of potential TRAE diarrhea is summarized in Fig 2.

Hypertension

Hypertension associated with an axitinib plus IO combination is more likely to be associated with axitinib rather than the IO agent. Continuous monitoring and early intervention with antihypertensive agents (such as calcium channel blockers or angiotensin-converting enzyme inhibitors) are recommended, with the goal of achieving a blood pressure of 120/80 to 140/95 mmHg.[27] The patient's blood

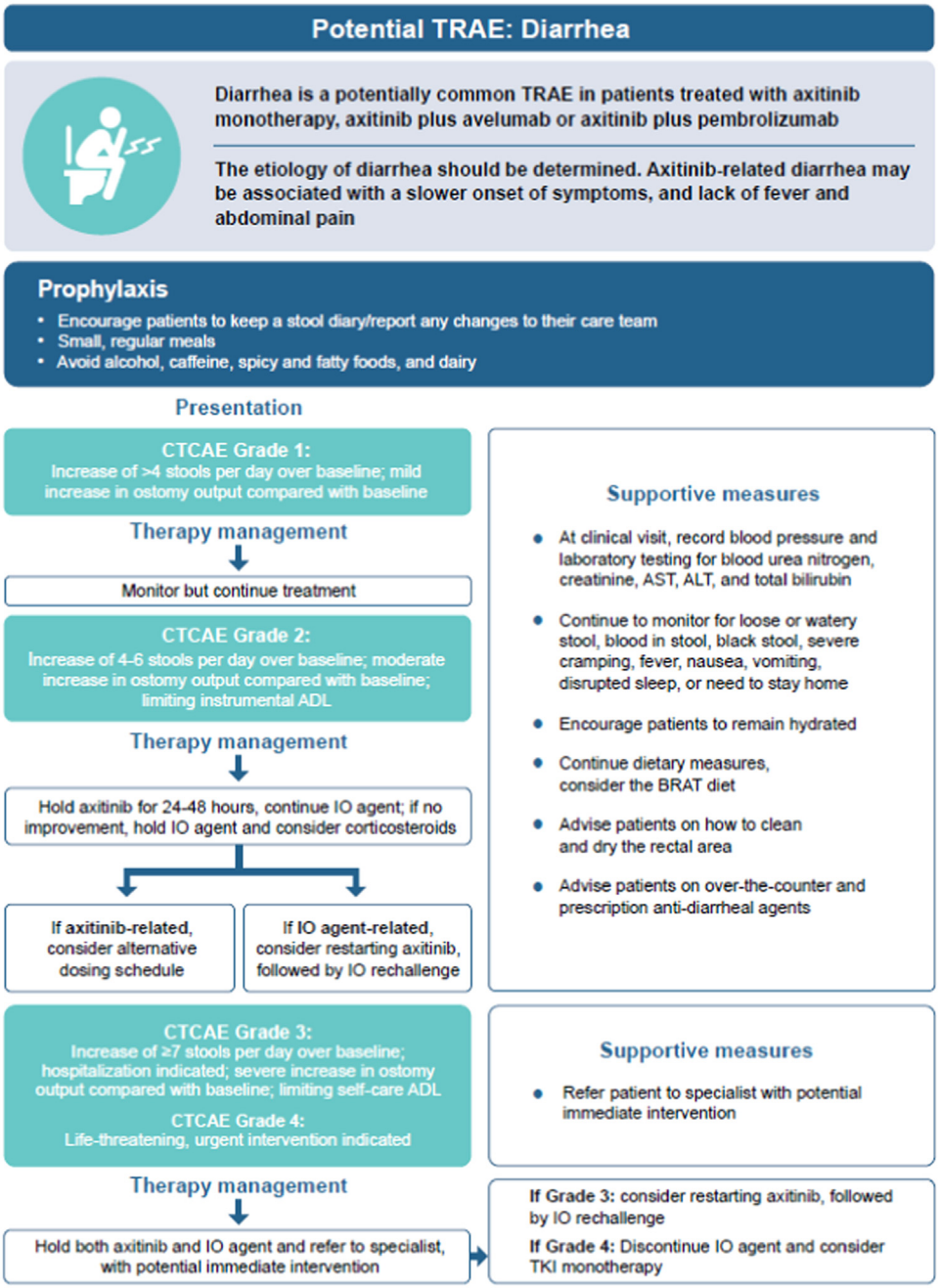

Fig 2. Management of potential TRAE diarrhea. ADL, activities of daily living; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BRAT, bananas, rice, applesauce, toast; CTCAE, Common Terminology Criteria for Adverse Events; IO, immuno-oncology; TRAE, treatment-related adverse event.

pressure should be well controlled prior to starting axitinib therapy and frequently monitored. Patients should be encouraged to take their own blood pressure regularly outside of clinical visits in order to detect hypertension events early.

Dose reduction of axitinib can occur and holding axitinib can result in hypotension in patients who had previously intensified their antihypertensive regimen.[27] Oncology nurses play a substantial role in the management of hypertension including, obtaining blood pressure measurements, patient education and counseling, detection, referral, and follow-up.[43,44] It is also vital that drug interactions with antihypertensives are reviewed and, with particular relevance for TKIs, CYP3A4 inhibitors should be avoided.[44,45] Management of potential TRAE hypertension is summarized in Fig 3.

Fatigue

Fatigue is particularly problematic to manage as it may be related to either the TKI or IO agent, the cancer itself, or endocrine dysfunction (eg, hypothyroidism). Once endocrine dysfunction and axitinib-related fatigue have been ruled out, other reversible causes and cancer-related fatigue should be considered.[27] Thorough endocrine surveillance throughout treatment should be carried out or triggered with the rapid onset or deterioration (within a few days) of fatigue symptoms, a gradual increase in fatigue during stable disease, and new or severe headache or visual impairment.[27]

Oncology nurses can have a positive impact on fatigue management; nurse-led monitoring and intervention for physical symptoms have been reported to alleviate fatigue in patients with advanced

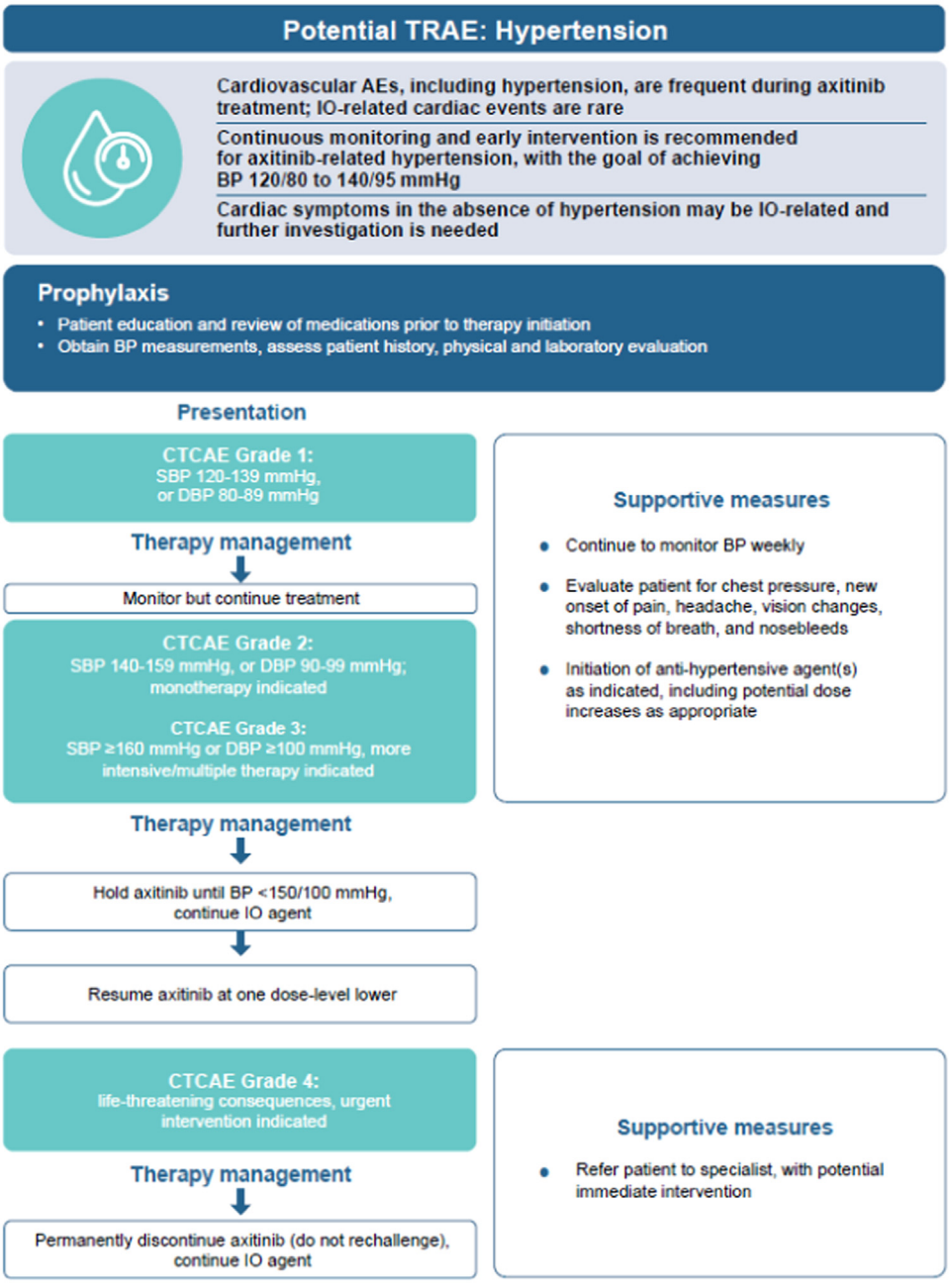

Fig 3. Management of potential TRAE hypertension. AE, adverse event; BP, blood pressure; CTCAE, Common Terminology Criteria for Adverse Events; DBP, diastolic blood pressure; IO, immuno-oncology; SBP, systolic blood pressure; TRAE, treatment-related adverse event.

cancer.[46] It is important to establish an in-depth fatigue history with the patient, including onset, pattern, duration, changes over time, alleviating factors, and contributing factors. Patient education is also important with regards to ensuring patients maintain an adequate diet and fluid intake. Discussing energy conservation can also be beneficial, allowing patients to set realistic expectations, and plans for a routine to allow activities at times of peak energy while factoring in pace, delegating activities, and rest.[47]

Oncology nurses can provide supportive care through patient education, referring the patient to a nutritionist, referral to a physical therapist and potentially psychological interventions, such as cognitive-behavioral therapy or counseling.[47] Management of potential TRAE fatigue is summarized in Fig 4.

Nausea/Vomiting

Nausea is a common symptom of many cancers and an AE of many treatments.[48] Supportive symptomatic care medications are often required to provide the patient comfort while on therapy. Patients should become self-aware of how nausea is affecting their eating, their ability to take in adequate fluids, or swallow medication, and if they are experiencing gagging. If a patient is experiencing one of these symptoms along with headache, hiccups, constipation, or anxiety, an over-the-counter antinausea medication should be considered. In addition, patients should consider taking sips of water, tea, ginger ale, or juices and eat small, frequent meals while avoiding strong odors or warm to hot food.

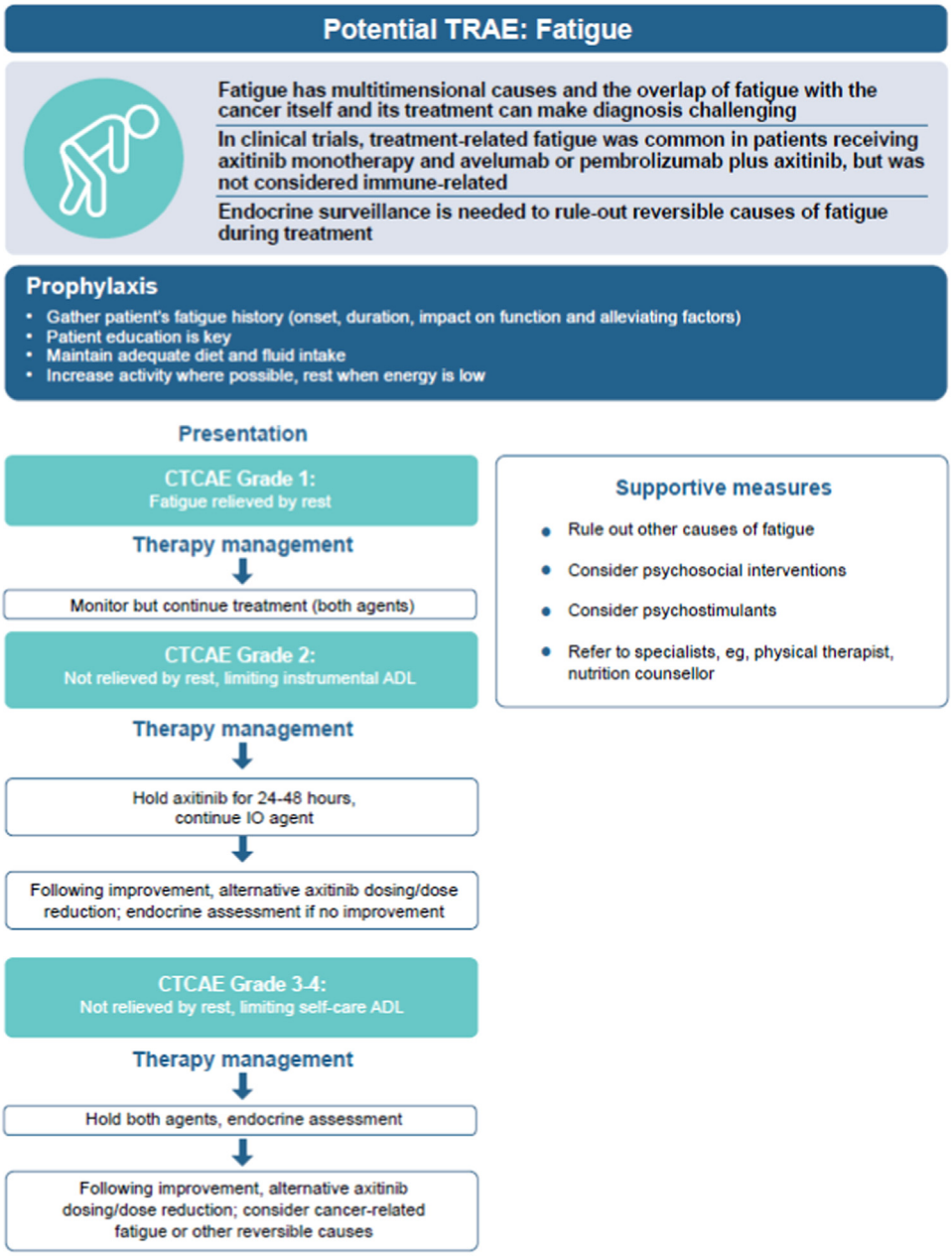

Fig 4. Management of potential TRAE fatigue. ADL, activities of daily living; CTCAE, Common Terminology Criteria for Adverse Events; IO, immuno-oncology; TRAE, treatment-related adverse event.

Hand-Foot Syndrome

Hand-foot syndrome often starts with a tingling feeling in the hands and feet; however, without proper intervention or treatment it can develop into diffuse redness, swelling, and even severe painful lesions that can prevent normal daily activities. Measures to prevent hand-foot syndrome are key to a patient's well-being. Patients should be encouraged to be self-aware of skin changes or feelings of pain/tingling in their hands and feet. As soon as a patient experiences even a small degree of burning, blistering, peeling, sores, bleeding, redness, swelling, tingling, itching, or difficulty using their hands/feet they should inform their care team. Prevention, early detection, and treatment of hand-foot syndrome will allow the patient to continue combination therapy, whereas waiting until the symptoms have significantly progressed may require the patient to permanently discontinue treatment.

Measures to prevent hand-foot syndrome include protecting the skin by avoiding irritation to the hand or foot. Patients should no longer walk barefoot but opt instead for soft slippers or cushioned shoes that reduce friction. In addition, they should avoid activities that may cause increased friction, such as jogging. Patients should avoid contact with harsh chemicals and extreme heat. Methods to reduce symptoms include cooling the hands and feet with ice packs or a cool towel for 15 to 20 minutes. Patients should also apply over-the-counter creams to their skin and consider urea-based creams if symptoms progress.

Conclusion

The emergence of IO agents (avelumab, ipilimumab, nivolumab, and pembrolizumab) and their use in combination with TKIs (axitinib, cabozantinib, and lenvatinib) marks a leap forward in the treatment of people with aRCC. With this advance in effective combination treatment options comes the complexity of managing overlapping TRAEs.

Oncology nurses and nurse-led innovations to monitor and assess treatments can have an impact on the management of AEs in cancer patients by identifying those patients who are most at risk, providing regular assessment, appropriate education, and supporting the monitoring of patient safety overall. Oncology nurses are part of a comprehensive team involving advanced practice providers, pharmacists, oncologists, and multidisciplinary specialists. Increasing use of combination regiments including oral TKIs and checkpoint inhibitors relies on oncology providers at all levels to increase their knowledge of potential side effects of individual drugs and the potential for overlapping and/or delayed toxicities. Patient education is particularly important in managing AEs and promoting self-care when people know what to expect, and how to seek the necessary help they may require. Oncology services must also be responsive and provide individualized patient support, including skilled oncology nurses, that can help address the supportive care needs (including AE monitoring) that are associated with novel cancer treatments. Early and ongoing communication from the patient and caregiver regarding the development of AEs is emphasized as a critical component of maximizing treatment outcomes and quality of life.

The goal of therapy in the treatment of aRCC is to provide patients with a durable deep response that leads to prolonged progression-free survival and ultimately overall survival. Without impactful treatment management initiatives and regular interactions with expert oncology nurses, patients may become nonadherent and/or discontinue treatment early. A patient will not likely experience the benefits of these effective treatment combinations if they end therapy prematurely. Oncology nurses play a critical role in ensuring patients maintain an acceptable quality of life and achieve the best possible treatment outcomes.

Declaration of competing interest

Sara Parreira, Kathleen Burns, Nancy Moldawer, Nazy Zomordian, Nesan Bandali, Kiran Virdee, Meghara Walsh and Laura Wood have no disclosures to report. Daniel Kelly is a member of a team of Grant Recipients from Pfizer to conduct an independent medical education program entitled "RCC4Nurses: Improving quality of nursing care in metastatic renal cell carcinoma" with the University of Glasgow and the European Oncology Nursing Society**.** Dharanija Rao and Rosemary Teresi are full-time employees and hold stock or stock options in Pfizer.

CRediT authorship contribution statement

Sara Parreira: Writing – review & editing, Conceptualization, Investigation. **Kathleen Burns:** Writing – review & editing, Conceptualization, Investigation. **Nancy Moldawer:** Writing – review & editing, Conceptualization, Investigation. **Nazy Zomordian:** Writing – review & editing, Conceptualization, Investigation. **Nesan Bandali:** Writing – review & editing, Conceptualization, Investigation. **Kiran Virdee:** Writing – review & editing, Conceptualization, Investigation. **Meghara Walsh:** Writing – review & editing, Conceptualization, Investigation. **Daniel Kelly:** Writing – review & editing, Conceptualization, Investigation. **Dharanija Rao:** Writing – review & editing, Conceptualization, Supervision. **Rosemary Teresi:** Writing – review & editing, Conceptualization, Supervision. **Laura S. Wood:** Writing – review & editing, Conceptualization, Investigation.

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Supplementary materials

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