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Expert Consensus Recommendations on the Management of Treatment-emergent Adverse Events Among Men with Prostate Cancer Taking Poly-ADP Ribose Polymerase Inhibitor + Novel Hormonal Therapy Combination Therapy

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Abstract

Background and objective: Recent clinical trials have shown improvement in progression-free survival in men with metastatic prostate cancer (mPC) treated with combination poly-ADP ribose polymerase (PARP) inhibitors (PARPi) and novel hormonal therapy (NHT). Regulatory bodies in the USA, Canada, Europe, and Japan have recently approved this combination therapy for mPC. Common adverse events (AEs) include fatigue, nausea and vomiting, and anemia. Nuanced AE management guidance for these combinations is lacking. The panel objective was to develop expert consensus on AE management in patients with mPC treated with the combination PARPi + NHT.

Methods: The RAND/University of California Los Angeles modified Delphi Panel method was used. AEs were defined using the Common Terminology Criteria for Adverse Events. Twelve experts (seven medical oncologists, one advanced practice registered nurse, three urologists, and one patient advocate) reviewed the relevant literature; independently rated initial AE management options for the agent suspected of causing the AE for 419 patient scenarios on a 1–9 scale; discussed areas of agreement (AoAs) and disagreement (AoDs) at a March 2023 meeting; and repeated these ratings following the meeting. Second-round ratings formed the basis of guidelines.

Key findings and limitations: AoDs decreased from 41% to 21% between the first and second round ratings, with agreement on at least one management strategy for every AE. AoAs included the following: (1) continue therapy with symptomatic treatment for

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patients with mild AEs; (2) for moderate fatigue, recommend nonpharmacologic treatment, hold treatment temporarily, and restart at a reduced dose when symptoms resolve; (3) for severe nausea or any degree of vomiting where symptomatic treatment fails, hold treatment temporarily and restart at a reduced dose when symptoms resolve; and (4) for hemoglobin 7.1–8.0 g/dl and symptoms of anemia, hold treatment temporarily and restart at a reduced dose after red blood cell transfusion.

Conclusions and clinical implications: This expert guidance can support management of AEs in patients with mPC receiving combination PARPi + NHT therapy.

Patient summary: A panel of experts developed guidelines for adverse event (AE) management in patients with metastatic prostate cancer treated with a combination of poly-ADP ribose polymerase inhibitors and novel hormonal therapy. For mild AEs, continuation of cancer therapy along with symptomatic treatment is recommended. For moderate or severe AEs, cancer therapy should be stopped temporarily and restarted at the same or a reduced dose when AE resolves.

1. Introduction

Metastatic prostate cancer (mPC) is one of the most common cancers among men, with an estimated 268 490 new cases and 34 500 deaths in 2022 in the USA. [58] Results from three recent clinical trials (PROpel—NCT03732820 [1], MAGNITUDE—NCT03748641 [2], and TALAPRO-2—NCT03395197 [3]) examining combination treatment of poly-ADP ribose polymerase (PARP) inhibitors (PARPi) and novel hormonal therapy (NHT) for men with prostate cancer have demonstrated clinical benefit, namely, improvement in radiographic progression-free survival [4–6]. Between May and August 2023, the U.S. Food and Drug Administration (FDA) approved three of these combination therapies for the treatment of patients with mPC. These included olaparib with abiraterone and prednisone (or prednisolone) for adults with BRCA-mutated metastatic castration-resistant prostate cancer, talazoparib with enzalutamide for *HRR* gene-mutated metastatic castration-resistant prostate cancer, and niraparib and abiraterone acetate plus prednisone for patients with BRCA-mutated mPC [7–9]. Between November 2022 and August 2023, a PARPi + NHT combination was also approved by the European Medicine Agency, the Pharmaceuticals and Medical Devices Agency (Japan), and Health Canada [10–12].

Treatment-emergent adverse events (TEAEs), including nausea and vomiting [13–16], anemia [17–20], increased aspartate transferase (AST) and/or alanine transaminase (ALT) [21,22], and fatigue occur in patients treated with PARPi across various cancers including prostate cancer. Fatigue is also a reported TEAE from NHT [23–25]. Across clinical trials, the most commonly reported TEAEs were anemia, fatigue, constipation, decreased hemoglobin (Hgb), neutrophils, platelets, laboratory abnormalities, and nausea [7–9]. To improve treatment outcomes and adherence, there is a need for nuanced guidance for clinicians on how to adequately manage TEAEs resulting from PARPi + NHT combination therapy in patients with mPC.

Our objective was to develop expert consensus on the initial management of TEAEs in patients with mPC treated with a combination of PARPi + NHT. To do so, a multidisciplinary and geographically diverse expert panel was convened using the RAND/University of California Los Angeles (UCLA) modified Delphi Panel method. This formal group consensus process systematically and quantitatively combines the latest clinical evidence with expert opinion to help health experts reach consensus on complex clinical topics [26–29]. In brief, the steps include a literature review, generation of a rating form, collection and analysis of first-round ratings from panelists, a professionally moderated in-person meeting where panelists discuss the areas of disagreement, final ratings and analysis of these ratings, and the development of a written summary of the areas of agreement [29].

2. Methods

The RAND/UCLA modified Delphi Panel method, originally developed by the RAND Corporation in the 1950s as a way to obtain group consensus on military decisions [30], relies on repeated, individual questioning of experts through surveys or "ratings." The methodology has since been adapted through partnership with UCLA for use in the medical setting [31]. The RAND/UCLA modified Delphi Panel method has been used extensively to develop medical society guidelines [32], other practice guidelines [33–37], disease classification systems [38], research agendas [39], and quality improvement interventions [27]. A recent systematic review identified 19 831 English-language peer-reviewed journal articles on the Delphi method published between 1950 and 2022 [40], with 12 883 in medical journals [40].

When used in the health care setting, rating forms completed by health experts include hundreds of hypothetical patient scenarios differing across clinically relevant characteristics [28]. The process of completing rating forms focuses on expert decision-making by encouraging granular thinking about whether each characteristic alone has an impact on their ratings [29]. Experts complete rating forms using a scale of 1 (highly inappropriate, risks outweigh benefits) to 9 (highly appropriate, benefits outweigh risks). During the discussion, experts are shown group medians and asked to explain their reasoning if their ratings fall out-

side of a certain range [29]. The group is never required to agree during the panel meeting. Instead, second-round ratings completed after the panel discussion are used as a summary of the group consensus, defined mathematically based on the number of low (ie, 1–3) versus high (ie, 7–9) ratings on the survey [28].

By avoiding certain cognitive biases [41] and harnessing the collection of knowledge of experts, guidelines developed using this method have content, construct, and predictive validity [29]. Results of modified Delphi panels conducted using the same evidence base produce similar results, and patients treated according to the resulting guidelines have been shown to have improved outcomes [42,43].

Using the modified Delphi Panel methodology, a rating form survey consisting of detailed patient scenarios was developed collaboratively by PHAR and panelists. In February 2023, before completing the ratings, panelists reviewed a summary of literature including European Society for Medical Oncology, American Society of Clinical Oncology (ASCO), and National Comprehensive Cancer Network (NCCN) guidelines on managing common adverse events (AEs) resulting from PARPi and NHT therapies across cancer types (eg, prostate, ovarian, and breast) [44–47]. Panelists then independently, electronically, and anonymously rated the appropriateness of various treatment interventions to manage initial TEAEs resulting from a combination of PARPi + NHT treatment across 367 unique clinical scenarios using the latest clinical evidence combined with their expert opinion. Panelists were sent the rating form at the same time and asked to return it on the same date. Severity across AEs was defined by Common Terminology Criteria for Adverse Events (CTCAE) v.3.0, 4.0, and 5.0, and NCCN guidelines [44,48–50].

For each clinical scenario, panelists rated the appropriateness of the intervention for treatment management on a scale of 1–9. Ratings between 1 and 3 were considered inappropriate, 7 and 9 appropriate, and 4 and 6 maybe appropriate (ie, it could be considered). Consensus for each rating form cell was reached when the number of panelists provided similar ratings within 1–3 and 7–9 together.

In March 2023, at a professionally moderated, in-person meeting, ten panelists (two were not able to attend) were provided their individual first-round ratings alongside the panel's median and range for all clinical scenarios. The expert panel process was organized and moderated by one of the authors (M.S.B.). Panelists shared the rationale behind their ratings, focusing on areas of disagreement. The moderator encouraged open discussion, but did not guide panelists to reach agreement. Following the meeting, all panelists virtually completed the rating form a second time across 419 unique clinical scenarios (increase from first-round form due to panelist-suggested edits to the rating form). A copy of the rating form results is available in the Supplementary material.

Ratings from the second-round survey were used to develop clinical recommendations, using the quantitative definitions of appropriateness provided above. In August 2023, these clinical recommendations were then circulated to all panelists for review and comment. All panelists approved the final consensus recommendations.

The panel of 12 experts included seven medical oncologists, one advanced practice registered nurse, three urologists, and one patient advocate. The advanced practice nurse and patient advocate were included to represent non-physicians who frequently interact with patients with mPC and to try and ensure a multidisciplinary panel with broad representation of the health care community [28,51]. A panel chair (N.A.) was appointed to help lead project efforts. Seven panelists were from the USA (IL, NC, NV, OH, PA, and UT), and five from other countries (two from Brazil and one each from Germany, Spain, and Japan). Panelists had an average of 16 yr of experience (range 4–34) and experience in treating and/or consulting patients with mPC (mean 179, range 60–325 in the past year).

All panelists except the panel chair received honoraria for their participation. Modified Delphi panels do not involve human individuals as defined by 45 CFR part 46,

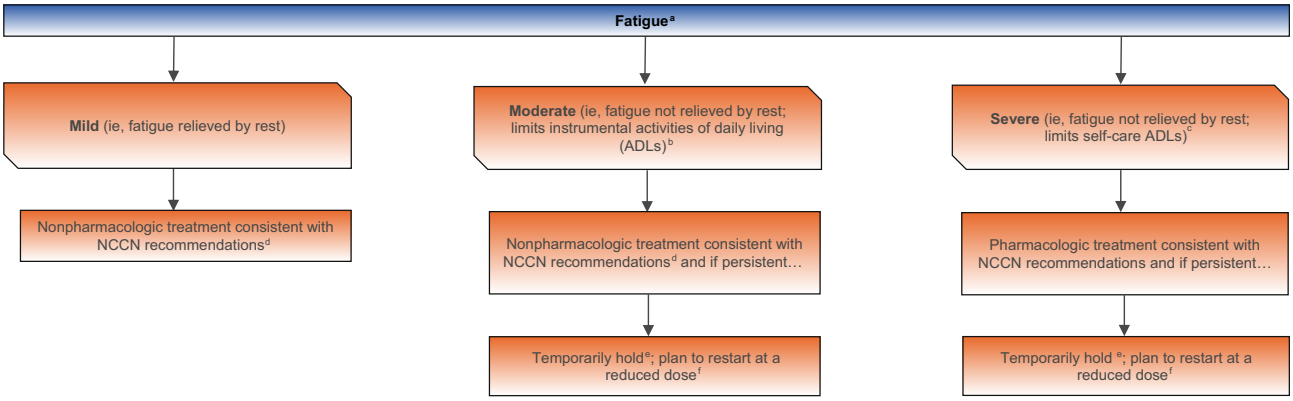

Fig. 1 – Fatigue management. ADL = activity of daily living; BT = behavioral therapy; CBT = cognitive behavioral therapy; CTCAE = Common Terminology Criteria for Adverse Events; NCCN = National Comprehensive Cancer Network; NHT = novel hormonal therapy; PARPi = poly-ADP ribose polymerase inhibitor. [a] Severity as defined by CTCAE v5.0; assume that the treating physician has determined the cause of the adverse event as NHT/PARPi treatment. [b] Instrumental ADLs refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. [c] Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden. [d] For example, physical activity, yoga, massage therapy, CBT, BT, psychoeducational therapies, and educational therapies. [e] Agent suspected of causing adverse event (eg, instruction does not apply to other part of combination therapy). [f] Restarting therapy depends on the patient's clinical status and relevant test results.

and therefore this study did not require an institutional review board approval.

3. Results

Panelists agreed on 59% (n = 367) of the round 1 and 78% (n = 419) of the round 2 ratings. Panelists rated clinical scenarios under the assumption that the AE in question was the patient's predominant AE, that other possible causes had been ruled out, and that patients would be amenable to the treatment recommendations.

In general, the panel recommends symptomatic treatment of all AEs before therapy is held or stopped, and specifically suggests careful consideration of the potential clinical benefit of treatment before discontinuation. The panel also encourages a shared decision-making process among the clinical team and the patient, particularly with regard to symptomatic AEs. The recommendations below are intended only as general guidance and in no way are intended to supersede that shared decision-making process. The absolute level of dose reduction and the length of time treatment should be held in response to an AE must be individualized. The guidance below is for PARPi + NHT combination therapies in general, and practitioners should refer to individual drug labels for PARPi, NHT, and other supportive therapies for more specific guidance including drug-drug interactions. The guidelines were developed considering the initial presentation of these AEs. Other interventions may be more appropriate if the AE persists or recurs after initial treatment.

3.1. *Fatigue*

The panel recommended nonpharmacologic (eg, physical activity) treatment consistent with NCCN guidelines [44] for patients with mild (fatigue relieved by rest) and moderate (fatigue not relieved by rest and limiting instrumental activities of daily living [ADLs]) fatigue, and pharmacologic treatment (eg, methylphenidate) consistent with NCCN guidelines [44] for patients with severe fatigue (fatigue not relieved by rest and limiting self-care ADLs). In patients with moderate and severe fatigue, the panel recommends holding cancer treatment temporarily, with a plan to restart at a reduced dose as needed, depending on the patient's clinical status (Fig. 1).

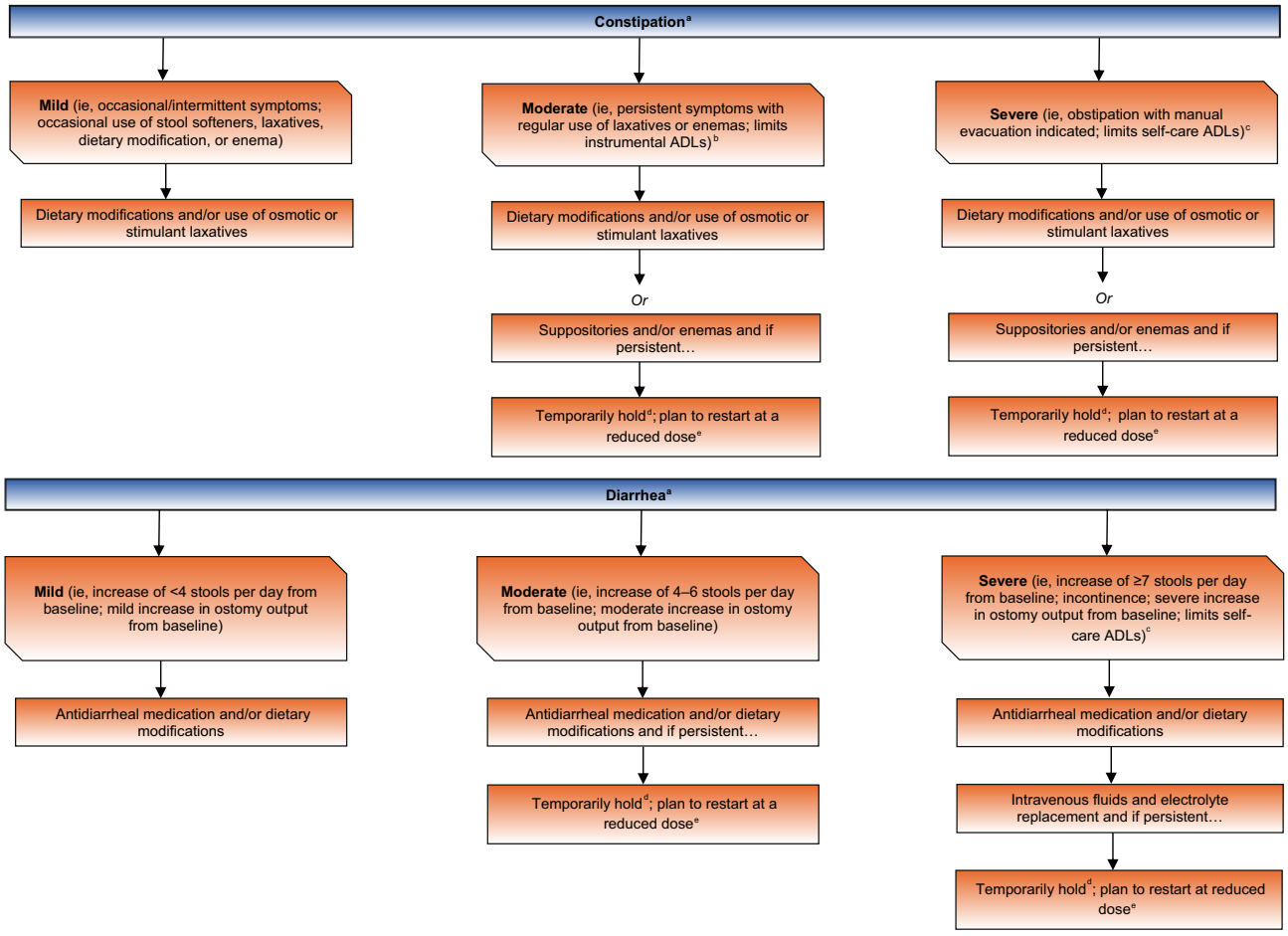

Fig. 2 – Constipation and diarrhea management. ADL = activity of daily living; CTCAE = Common Terminology Criteria for Adverse Events; NHT = novel hormonal therapy; PARPi = poly-ADP ribose polymerase inhibitor. [a] Severity as defined by CTCAE v4.0 and v5.0; assume that the treating physician has determined the cause of the adverse event as NHT/PARPi treatment. [b] Instrumental ADLs refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. [c] Self-care ADLs refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden. [d] Agent suspected of causing adverse event (eg, instruction does not apply to other part of combination therapy). [e] Restarting therapy depends on the patient's clinical status and relevant test results.

3.2. Gastrointestinal AEs

3.2.1. Constipation

The panel recommends dietary modifications and/or use of osmotic or stimulant laxatives as the primary treatment for patients with mild constipation (occasional or intermittent symptoms with occasional use of stool softeners, laxatives, dietary modifications, or enemas). For patients with moderate (persistent symptoms with regular use of laxatives or enemas limiting instrumental ADLs) and severe (obstipation with manual evacuation indicated, limiting self-care ADLs) constipation, the panel recommended the use of suppositories and/or enemas as well as holding cancer treatment temporarily with a plan to restart at a reduced dose, if symptomatic treatment fails (Fig. 2).

3.2.2. Diarrhea

The panel recommends antidiarrheal medication and/or dietary modifications for all patients with diarrhea (an increase of up to four stools per day from baseline or mild increase in ostomy output from baseline) [8,9]. In patients with moderate (an increase of four to six stools per day from baseline or moderate increase in ostomy output from baseline) and severe (an increase of seven or more stools per day from baseline, incontinence, severe increase in ostomy output from baseline, or limiting self-care ADLs) diarrhea, the panel recommends intravenous fluids and electrolyte replacement as well as holding cancer therapy temporarily with a plan to restart at a reduced dose if needed and as the clinical situation permits (Fig. 2).

3.2.3. Nausea and vomiting prophylaxis

The panel recommends patients with one or more risk factors (including therapy-induced nausea and/or vomiting in a prior treatment cycle, younger age, proneness to motion sickness, and/or anxiety or high pretreatment expectation of disease) [44] receive prophylaxis consistent with NCCN antiemesis guidelines, which include either the use of one 5-HT3-RA and dexamethasone for agents of moderate to high emetic risk or the use of metoclopramide or prochlorperazine for agents of minimal to low emetic risk [44].

3.2.4. Nausea

The panel recommends that patients with mild (loss of appetite without alteration in eating habits) or moderate (decrease in oral intake without significant dehydration or weight loss) nausea receive pharmacologic treatment consistent with NCCN [44] and/or ASCO guidelines [52] for nau-

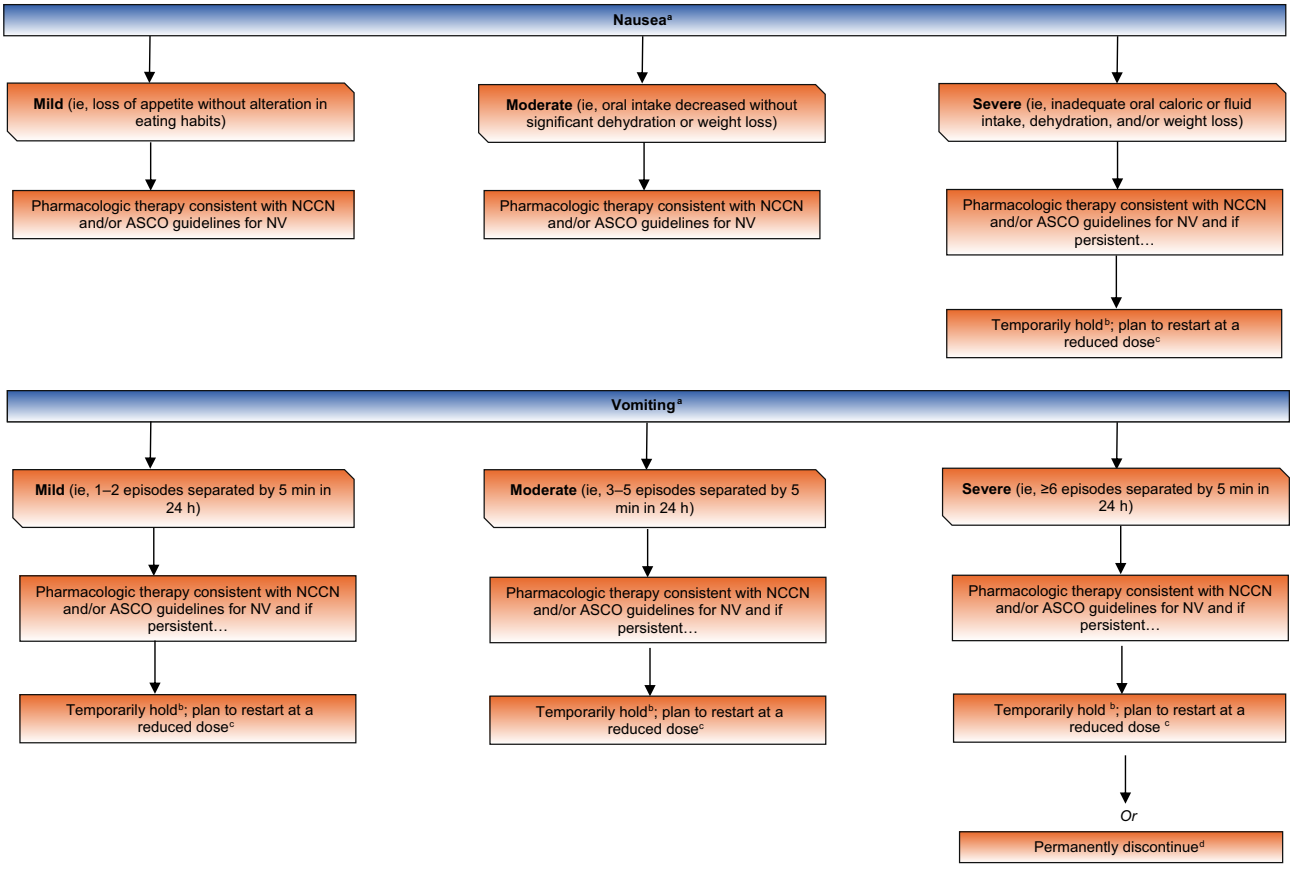

Fig. 3 – Nausea and vomiting management. ASCO = American Society of Clinical Oncology; CTCAE = Common Terminology Criteria for Adverse Events; NCCN = National Comprehensive Cancer Network; NHT = novel hormonal therapy; NV = nausea and vomiting; PARPi = poly-ADP ribose polymerase inhibitor. [a] Severity as defined by CTCAE v4.0 and v5.0; assume that the treating physician has determined the cause of the adverse event as NHT/PARPi treatment. [b] Agent suspected of causing adverse event (eg, instruction does not apply to other part of combination therapy). [c] Restarting therapy depends on the patient's clinical status and relevant test results. [d] Treatment discontinuation must be weighed carefully against the potential clinical benefit, particularly among patients who are BRCA1/2 positive.

sea. For patients with severe nausea (inadequate oral caloric or fluid intake, dehydration, and/or weight loss), the panel recommends considering holding cancer therapy temporarily with a plan to restart at a reduced dose if needed and depending upon individual patient circumstances (Fig. 3).

3.2.5. *Vomiting*

For patients experiencing treatment-emergent nausea and vomiting, the panel recommends the use of ondansetron as a first-line agent. The panel recommends ondansetron and prochlorperazine as second- or third-line agents, and metoclopramide as a third-line agent. For all patients with vomiting (mild vomiting was defined as one to two episodes separate by 5 min in 24 h; moderate vomiting was defined as three to five episodes separated by 5 min in 24 h) [15], if symptomatic measures fail, the panel recommends holding cancer therapy temporarily with a plan to restart at a reduced dose. In patients with severe vomiting (six or more episodes separated by 5 min in 24 h), the panel recommends consideration to be given to permanently discontinuing cancer treatment, weighing this decision carefully against the potential benefit of continued treatment (Fig. 3).

3.3. *Hematologic AEs*

3.3.1. *Anemia*

The panel generally recommends no treatment and no change in cancer therapy for stable, asymptomatic patients with mild anemia (Hgb 8.10–10.0 g/dl). For stable and asymptomatic patients with moderate anemia (Hgb 7.1–8.0 g/dl), the panel recommends holding cancer therapy temporarily with a plan to restart at a reduced dose when anemia improves. Unstable or symptomatic patients with moderate anemia, as well as any patients with severe anemia (Hgb $\leq$7 g/dl), should also receive red blood cell transfusion, consistent with institutional guidelines, and have treatment held. Permanent discontinuation of cancer treatment is recommended in cases of persistent severe anemia and should be considered in those with moderate anemia who are clinically unstable or symptomatic (Fig. 4).

3.3.2. *Neutropenia*

In patients with an absolute neutrophil count (ANC) >1000 ml but below the lower limit of normal, the panel recommends individualizing treatment based on clinical circumstances and laboratory test results, and considering holding cancer therapy temporarily if the patient is febrile or has evidence of infection. In afebrile patients with ANC 501–1000 ml whose white count is not declining rapidly, the panel recommends holding cancer therapy temporarily with a plan to restart when the white count recovers. In patients with ANC 501–1000 ml with fever or in patients whose ANC is predicted to fall below 500 in the next 48 h, the panel recommends restarting at a reduced dose. Permanent discontinuation of cancer treatment can be considered in patients with persistent ANC levels of 501–1000 or $\leq$500 ml (Fig. 5).

3.3.3. *Thrombocytopenia*

For all patients with platelets <75 000/mm^3, the panel recommends holding cancer therapy temporarily with a plan to restart at a reduced dose. In severe thrombocytopenia

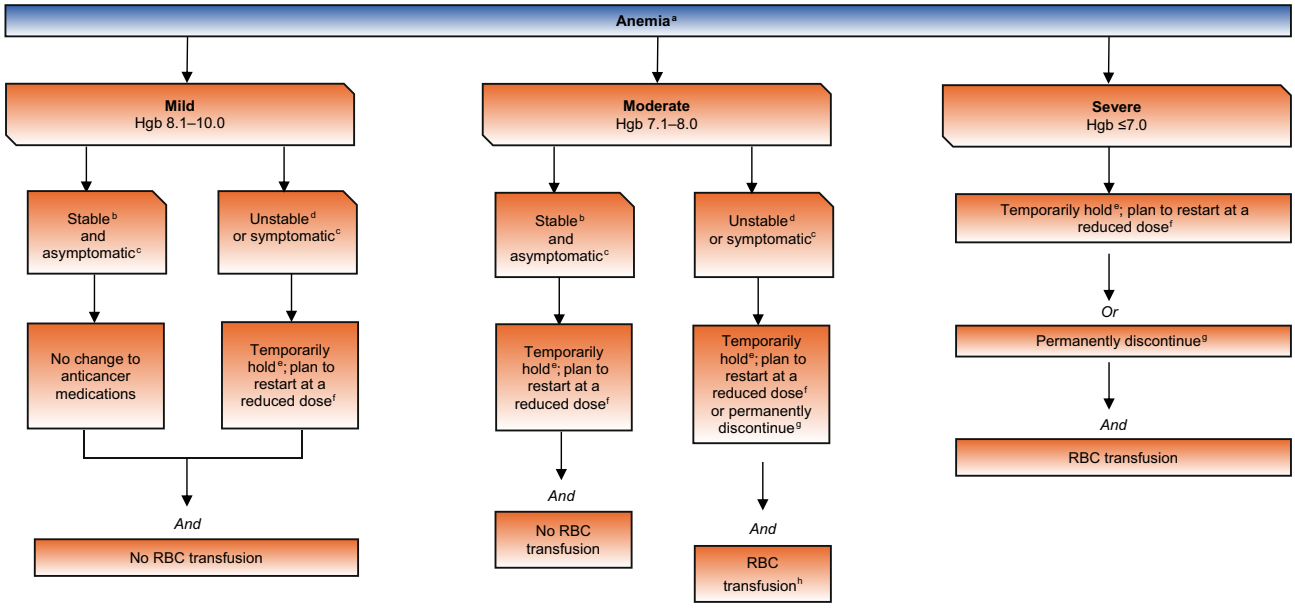

Fig. 4 – Anemia management. CTCAE = Common Terminology Criteria for Adverse Events; Hgb = hemoglobin; NCCN = National Comprehensive Cancer Network; NHT = novel hormonal therapy; PARPi = poly-ADP ribose polymerase inhibitor; RBC = red blood cell. [a] Modified from CTCAE v5.0; assume that the treating physician has determined the cause of the adverse event as NHT/PARPi treatment. [b] For example, unchanged or <2 g/dl pretreatment baseline. [c] Symptoms can include fatigue, weakness, pale skin, chest pain, fast heartbeat or shortness of breath, headache, dizziness, lightheadedness, cold hands and feet, and loss of appetite (NCCN). [d] For example, falling >2 g/dl pretreatment baseline. [e] Agent suspected of causing adverse event (eg, instruction does not apply to other part of combination therapy). [f] Restarting therapy depends on the patient's clinical status and relevant test results. [g] Treatment discontinuation must be weighed carefully against the potential clinical benefit, particularly among patients who are BRCA1/2 positive. [h] Among patients who are asymptomatic with no comorbidities (eg, cardiac disease, chronic pulmonary disease, or cerebral vascular disease [NCCN]), RBC transfusion may not be necessary.

(ie, platelets <25 000/mm^3 (<25.0 × 109/l), it is appropriate to consider discontinuing cancer treatment permanently (Fig. 5).

3.4. Elevated laboratory values

3.4.1. ALT and AST

In patients with mild ALT and AST elevation (ie, >upper limit of normal [ULN] – 3.0 × ULN), the panel recommends considering holding cancer therapy temporarily depending on individual patient circumstances and pursuing workup to rule out any unrelated cause of elevated liver enzymes. For patients with moderate elevation (ie, >3.0–5.0 × ULN), the panel recommends holding cancer therapy temporarily with the decision to restart at a reduced dose depending on the patient's clinical status and relevant test results. In patients with a more severe elevation (ie, >5.0–20.0 × ULN), the panel recommends holding cancer therapy temporarily with the decision to restart at a reduced dose depending on the patient's clinical status and relevant test results. For patients with a severe elevation (ie, >20 × ULN), the panel recommends considering permanent discontinuation of cancer treatment (Fig. 6).

3.4.2. Creatinine

The panel recommends patients with mild to moderately elevated creatinine (ie, >1.5–6.0 times ULN) have their cancer therapy held temporarily with a plan to restart at a reduced dose. In patients with severely elevated creatinine (ie, >6.0 times ULN), the panel recommends considering permanently discontinuing cancer treatment (Fig. 6).

4. Discussion

Following a literature search in December 2022, a gap in available evidence on the management of PARPi + NHT combination therapy TEAEs was identified, immediately following an approval for that combination therapy in Europe and on the cusp of approvals for such combination treatments in the USA, Japan, and Canada. Our objective was to develop expert consensus on the management of these TEAEs to supplement published data and guidelines. After reviewing the current literature, expert panelists rated 367 unique clinical scenarios in the first round and 329 in the second round in March 2023. Experts developed guidance on initial management of TEAEs resulting from PARPi and NHT treatment in men with prostate cancer. In general,

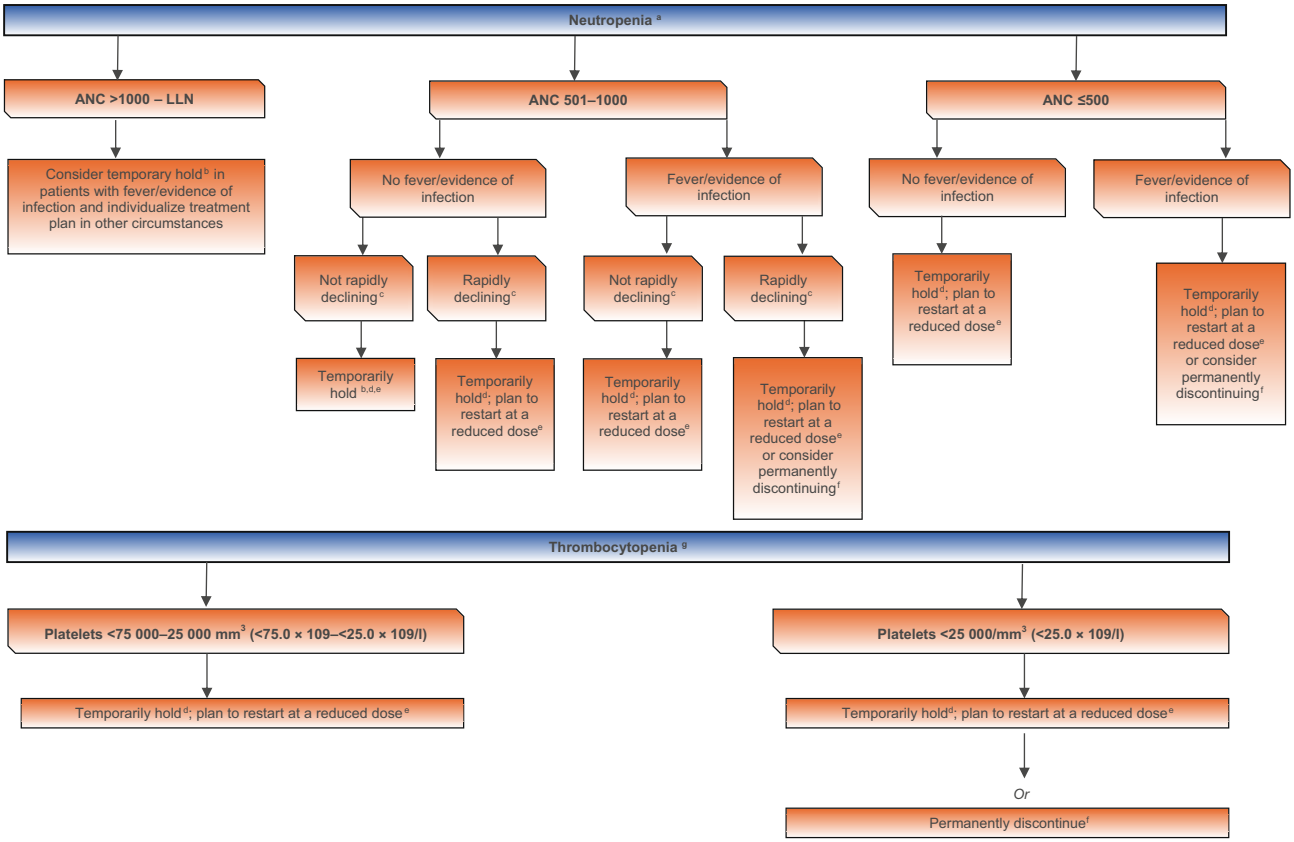

Fig. 5 – Neutropenia and thrombocytopenia management. ANC = absolute neutrophil count; CTCAE = Common Terminology Criteria for Adverse Events; LLN = lower limit of normal; NCCN = National Comprehensive Cancer Network; NHT = novel hormonal therapy; PARPi = poly-ADP ribose polymerase inhibitor. [a] Severity as defined by NCCN; assume that the treating physician has determined the cause of the adverse event as NHT/PARPi treatment. [b] The decision to restart at the same or a reduced dose depends on individual patient circumstances. [c] Predicted to decline to ≤500 neutrophils/μl over the next 48 h. [d] Agent suspected of causing adverse event (eg, instruction does not apply to other part of combination therapy). [e] Restarting therapy depends on the patient's clinical status and relevant test results. [f] Treatment discontinuation must be weighed carefully against the potential clinical benefit, particularly among patients who are BRCA1/2 positive. [g] Severity defined by CTCAE v3.0, blood and bone marrow adverse events, platelets, 2006; assume that the treating physician has determined the cause of the adverse event as NHT/PARPi treatment.

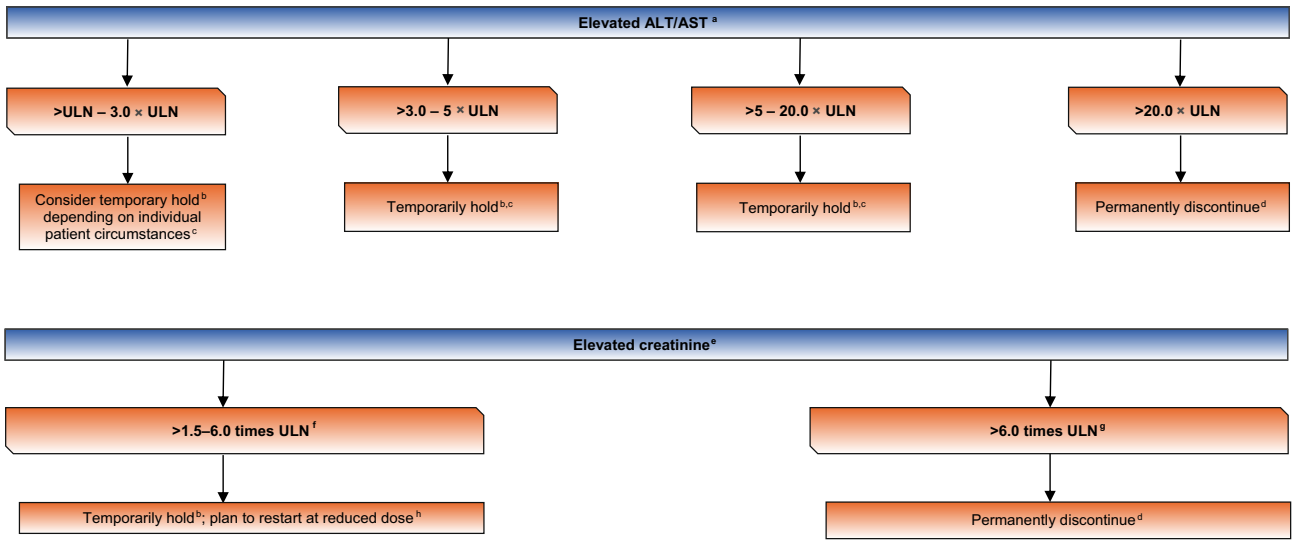

Fig. 6 – Elevated ALT/AST and creatinine management. ALT = alanine transaminase; AST = aspartate transferase; CrCl = Creatinine clearance; CTCAE = Common Terminology Criteria for Adverse Events; eGFR = estimated glomerular filtration rate; NHT = novel hormonal therapy; PARPi = poly-ADP ribose polymerase inhibitor; ULN = upper limit of normal. [a] Severity defined by CTCAE v5.0; assume that the treating physician has determined the cause of the adverse event as NHT/PARPi treatment. [b] Agent suspected of causing adverse event (eg, instruction does not apply to other part of combination therapy). [c] Restarting therapy depends on the patient's clinical status and relevant test results; the decision to restart at the same or a reduced dose depends on individual patient circumstances. [d] Treatment discontinuation must be weighed carefully against the potential clinical benefit, particularly among patients who are BRCA1/2 positive. [e] Severity defined by CTCAE v5.0; assume that the treating physician has determined the cause of the adverse event as NHT/PARPi treatment. [f] eGFR or CrCl 59–15 ml/min/1.73 m^2. [g] Restarting therapy depends on the patient's clinical status and relevant test results. [h] eGFR or CrCl <15 ml/min/1.73 m^2; dialysis or renal transplant indicated.

for mild TEAEs, the panel recommends continuing cancer therapy and providing symptomatic or supplementary treatment. For more severe TEAEs, the panel recommends holding treatment temporarily and restarting either at the same or at a reduced dose when the AE resolves.

The findings of the panel are consistent with the existing NCCN guidelines and previously published treatment recommendations for toxicities resulting from PARPi. The panel incorporated NCCN recommendations for the treatment of nausea, vomiting, and anemia into the guidance and made PARPi + NHT-specific guidance where appropriate. To generate panel recommendations, the RAND/UCLA modified Delphi Panel method, a well-established expert consensus methodology, was used [53,54]. In addition to expert physicians, the panel included an advanced practice registered nurse and a patient advocate, consistent with the goal of having broad representation of the relevant health care community [51].

Our study has limitations. First, the method relies on expert opinion informed by evidence and experience. While all panelists had experience treating and/or consulting patients with mPC, and represented various practice settings and clinical backgrounds, 12 people cannot represent the entire experience of those who work in this field. Nonetheless, the number of experts falls within the recommended guideline panel size of 7–15 [28] and represents panelists from various clinical backgrounds who have experience treating and/or managing patients on PARPi + NHT combination therapy. The method has content, construct, and predictive validity [29], and RAND/UCLA modified Delphi panels have been used to develop medical society guidelines [32], practice guidelines [33–37], and quality improvement interventions [27]. Second, management categories of the agent suspected of causing the AE were broad (eg, "immediate dose reduction without a prior hold"). Doing this allowed us to capture overarching agreement and disagreement within the panel as to whether such actions were appropriate across varying scenarios. As a result, however, the panel did not discuss specific numerical dose modifications. Third, rare and serious AEs (eg, thromboembolic events) were not the focus of this panel. Lastly, our study focused on the AE profile of PARPi in the context of combination therapy regimens of PARPi + NHT. As such, the AE profile discussed was focused primarily on those resulting from PARPi. However, we acknowledge the varied AE profiles resulting from NHTs [55–57]. The objective of developing these panel recommendations, shaped by currently available literature and expert opinion, is to improve the quality of care for patients with mPC on a combination of PARPi and NHT therapy.

5. Conclusions

These recommendations are based on the currently available evidence and reflect the agreement of a group of expert medical oncologists, urologists, an advanced practice registered nurse, and a patient advocate. These recommendations can be a helpful guide to physicians treating patients with mPC to manage the variety of AEs resulting from PARPi + NHT combination treatments. Future studies should aim to understand how these recommendations impact patient care and outcomes once integrated into clinical practice.

This study was presented in the poster session of the 15th European Multidisciplinary Congress on Urological Cancers (EMUC23), November 2–5, 2023, Marseille, France.

***Author contributions*:** Neal D. Shore and Michael S. Broder had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: Shore, Niyazov, Shaman, Zielinski, Chang, Agarwal.
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Appendix A. Supplementary data

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