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Immune Checkpoint Inhibitors in Advanced Renal Cell Carcinoma: Examining the Impact of Nutritional Status, Inflammation, and Body Composition

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ABSTRACT

Renal Cell Carcinoma (RCC) is among the most frequently diagnosed cancers in the United States. One-third of patients present with metastatic disease, and up to another half may progress to metastasis following surgical treatment. Survival rates for metastatic RCC have risen over the past 20 years, an improvement partially attributable to the increased availability of immune checkpoint inhibitors (ICI). However, mRCC remains a fatal genitourinary cancer, with patients often demonstrating both primary and secondary resistance to available immunotherapies. Sarcopenia, inflammation and nutrition have emerged as important prognostic factors in RCC. Recent studies have demonstrated their impact in predicting efficacy and tolerability of ICIs for RCC and other advanced solid malignancies. In this review, we aim to highlight the major milestones in ICI therapy for RCC, and associated mechanisms of action. We also examine how sarcopenia, inflammation and nutrition affect outcomes in RCC, particularly with consideration of the impact on immunotherapy efficacy and toxicity.

KEYWORDS: Kidney Cancer, metastatic renal cell carcinoma, immunotherapy, systemic therapy, sarcopenia, nutrition, inflammation

INTRODUCTION

Renal Cell Carcinoma (RCC) is among the top 10 cancer diagnoses in the United States, with an estimated 79,000 new cases and 14,000 deaths in 2022.[1] The incidence has doubled over the past half-century, likely attributed to improved and more frequent imaging.[2] Nevertheless, one-third of patients present with distant metastatic disease and 20-50% progress to metastasis despite surgical resection.[3] Over the past decade, the 5-year survival rate for metastatic RCC (mRCC) has risen from 12% to 15.3%,[1,3] an improvement at least partially attributed to the increased availability of systemic treatment options. Primary systemic therapy options for RCC include vascular endothelial growth factor (VEGF)-targeted tyrosine kinase inhibitors (TKI) and the more recent introduction of immune checkpoint inhibitors (ICI) such as nivolumab, ipilimumab, pembrolizumab and avelumab. The development of immune checkpoint blockade with antibodies against programmed cell death protein 1 (PD-1), programmed cell death ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) has resulted in significant and durable responses in RCC with acceptable safety.[4–10] Multiple phase III randomized clinical trials comparing ICI monotherapy and combination therapies against targeted therapies for RCC have demonstrated higher median overall survival (OS) and progression-free survival (PFS) with improved objective response rates (ORR).[4–8,11] This has resulted in a major shift towards ICI-based combination therapies as preferred, first-line options for the management of advanced RCC.[12]

However, ICI efficacy and tolerance may be impacted by other factors, such as sarcopenia, inflammation, and nutritional status, which influence survival outcomes in patients with cancer. Sarcopenia is a progressive and generalized

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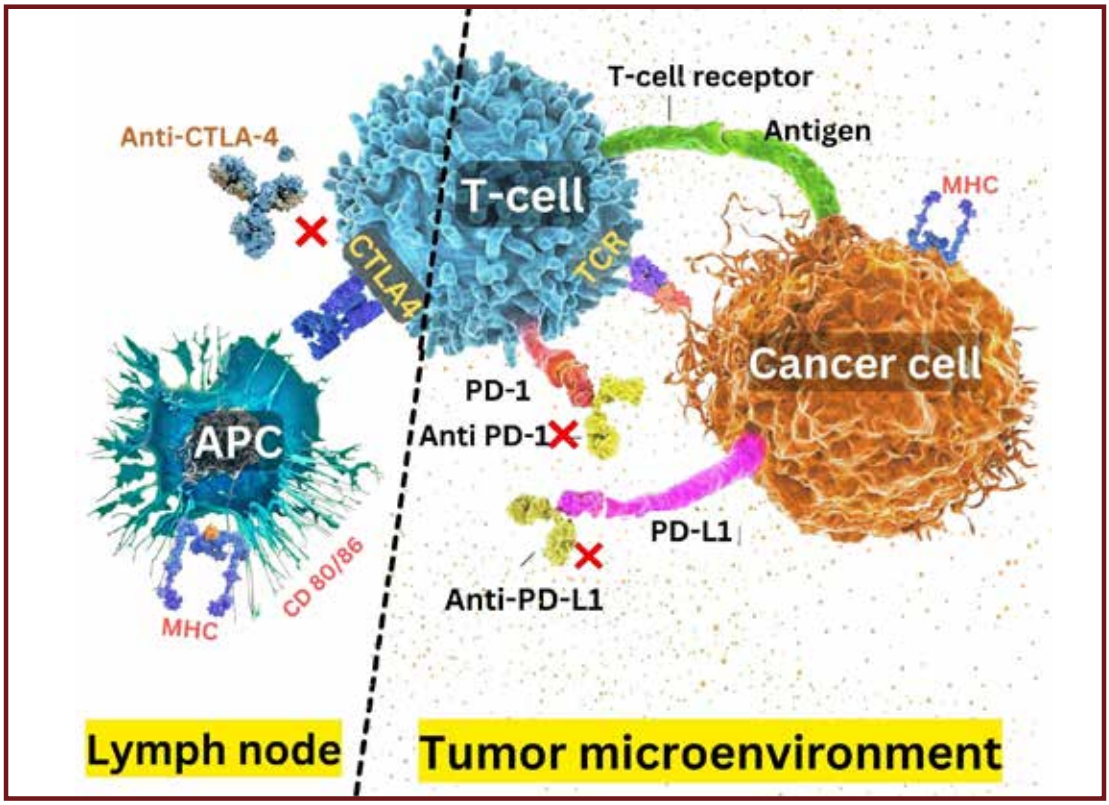

FIGURE 1 | Mechanism of Immune Checkpoint Antibody Blockade in RCC. Abbreviations: Programmed Cell Death Protein 1 (PD-1), Programmed Cell Death Ligand 1 (PD-L1), Cytotoxic T-Lymphocyte-associated Antigen 4 (CTLA-4), T-Cell Receptor (TCR), Antigen Presenting Cell (APC), Major Histocompatibility Complex (MHC), Cluster of Differentiation 80/86 (CD80/86)

skeletal muscle disorder with accelerated loss of muscle mass and function associated with increased risk of falls, frailty, and mortality.[13] Although observed in the context of aging, sarcopenia additionally occurs concurrently or independently in the setting of cancer,[14,15] where there is malignancy-related weight loss and muscle wasting known as cancer cachexia.[16] Sarcopenia and its association with worse survival has been widely reported in patients with RCC, especially in patients with advanced or metastatic disease.[14,17–24] Similarly, markers of malnutrition and inflammation, such as C-reactive protein (CRP), low body mass index (BMI), hypoalbuminemia and neutrophil, lymphocyte, and platelet counts, have also been associated with survival in RCC and other malignancies.[25–29]

In addition to influencing survival in RCC, studies have documented the impact of these factors on the efficacy and tolerability of ICI treatment. Here, we briefly review the major milestones in ICI therapy for advanced RCC and associated mechanisms of action. We focused on data from clear cell RCC as the most commonly encountered histology, recognizing that much of our management of non-clear cell subtypes are extrapolated from this body of work. Then, we examine sarcopenia, inflammation, and malnutrition in RCC and consider its impact on immunotherapy efficacy and tolerance and discuss future considerations for guiding management.

IMMUNE CHECKPOINT INHIBITORS IN ADVANCED RENAL CELL CARCINOMA

Numerous immunotherapies have been studied and received approval for treatment of RCC since 2015. A representative summary of these randomized controlled trials are summarized in **Table 1**. A summary of the mechanism of immune checkpoint inhibition is also represented in **Figure 1**.

History of Immune Checkpoint Inhibitors

The FDA approved the first ICI, ipilimumab (CTLA-4 checkpoint inhibitor), in 2011 for metastatic melanoma.[30,31] Then, in 2014, the FDA approved the first PD-1 checkpoint inhibitor, nivolumab.[30,31] The phase 3 CheckMate 025 trial, published in 2015, compared nivolumab versus everolimus in mRCC following prior treatment, which demonstrated longer median OS (25.0 months [95% confidence interval, 21.8 to not estimable] vs 19.6 months [95% CI, 17.6-23.1]) with less grade 3-4 treatment related adverse events (TRAE), but no difference in progression free survival (PFS, 4.6 [95% CI, 3.7-5.4] vs 4.4 months [95% CI, 3.7-5.5]).4 Nivolumab for the treatment of mRCC after treatment with standard antiangiogenic therapy was then approved. Combination therapy of nivolumab plus ipilimumab versus sunitinib in previously untreated mRCC was studied in the phase III

Clinical Trial	Patient Population	Number of Patients	Treatment Arms	Primary Outcome(s)
CheckMate 025[4]	mRCC following prior treatment	821	1. Nivolumab 2. Everolimus	OS
CheckMate 214[5]	Untreated advanced ccRCC	1096	1. Nivolumab + Ipilimumab 2. Sunitinib	OS, PFS, ORR - among IMDC poor/intermediate risk groups
KEYNOTE-426[11]	Untreated advanced ccRCC	861	1. Pembrolizumab + Axitinib 2. Sunitinib	OS, PFS - in intention-to-treat population
JAVELIN Renal 101[6]	Untreated advanced RCC	886	1. Avelumab + Axitinib 2. Sunitinib	PFS, OS - among PD-L1 positive tumors
CheckMate 9ER[7]	Untreated advanced ccRCC	651	1. Nivolumab + Cabozantinib 2. Sunitinib	PFS
CLEAR[8]	Untreated advanced RCC	1069	1. Lenvatinib + Pembrolizumab 2. Lenvatinib + Everolimus 3. Sunitinib	PFS

TABLE 1 | Summary of Randomized, Open-label, Phase 3 Clinical Trials of FDA-Approved Immunotherapies for RCC

Checkmate 214 trial. This showed significantly longer OS (median OS not reached [95% CI, 28.2 months to not estimable] versus 26.0 months [95% CI, 22.1 to not estimable]), higher objective response rate (ORR, 42% [95% CI, 37-47] vs 27% [95% CI, 22-31], p<0.0001) and complete response rate (CRR, 9% vs 1%), which led to FDA approval as first-line treatment for intermediate to poor-risk advanced RCC in April 2018.[5,31] In the long-term analysis with minimum 42-month follow-up, duration of response was longer, and more patients achieved complete response with nivolumab plus ipilimumab regardless of International mRCC Database Consortium (IMDC) risk group.[32]

Pembrolizumab, another PD-1 checkpoint inhibitor, was first approved in 2014 for advanced melanoma, and showed antitumor activity in untreated mRCC.[33] The KEYNOTE-426 trial comparing pembrolizumab plus axitinib, an anti-VEGF TKI, versus sunitinib for treatment-naive advanced ccRCC showed a 12-month OS benefit (89.9% [95% CI, 86.4-92.4] vs 78.3% [95% CI, 73.8-82.1]) with a longer PFS (15.1 [95% CI, 12.6-17.7] vs 11.1 months [95% CI, 8.7-12.5]) and improved ORR (59.3% [95% CI, 54.5-63.9] vs 35.7% [95% CI, 31.1-40.4], p<0.001). These results were observed across all IMDC risk groups regardless of PD-L1 expression.[11] FDA approval followed soon after in April 2019 as first-line combination immunotherapy for all-risk advanced RCC.

The first PD-L1 checkpoint inhibitor that received approval for mRCC was avelumab with combination axitinib in May 2019. This was supported by the phase III JAVELIN Renal 101 trial of avelumab plus axitinib as compared with sunitinib in patients with previously untreated advanced RCC. Primary endpoints focused on PFS and OS among patients with PD-L1 positive tumors. The median PFS among this cohort was significantly longer for patients that received avelumab plus axitinib (13.8 [95% CI, 11.1 to not estimable] vs 7.2 months [95% CI, 5.7-9.7]), and in the overall population, PFS was also longer (13.8 [95% CI, 11.1 to non estimable] vs 8.4 months [95% CI, 6.9-11.1]).[6]

In 2021, the FDA granted approval to the two remaining frontline combination immunotherapies for advanced RCC treatment: cabozantinib (TKI) plus nivolumab, and lenvatinib (TKI) plus pembrolizumab. The phase III CheckMate 9ER trial comparing nivolumab plus cabozantinib versus sunitinib for advanced RCC showed benefits in median PFS (16.6 [95% CI, 12.5-24.9] vs 8.3 months [95% CI, 7.0-9.7]) and ORR (55.7% [95% CI, 50.1-61.2] vs 27.1% [95% CI, 22.4-32.3], p<0.001). Grade 3 or higher TRAEs were similar, with patients also reporting better health-related quality of life with the combination regiment, demonstrating its acceptable safety profile.[7] In the CLEAR trial comparing lenvatinib plus pembrolizumab or everolimus versus sunitinib for advanced RCC, significant benefits were observed with the immunotherapy-containing regimen in terms of PFS (23.9 [95% CI, 20.8-27.7] vs 9.2 months [95% CI,

Reference	Tumor Type	Treatment	Prognostic Parameters (units)	Primary Outcomes	Results
Loosen et al 2021[72]	NSCLC, Melanoma, UC, GI, Head and Neck, Other	Nivolumab, Pembrolizumab, Nivolumab + Ipilimumab, Others	ΔL3-SMI (mm^2/cm), MMA (HU)	ORR, OS, PFS	OS, PFS significantly lower in ΔSMI <-6.18, ΔMMA <0.4
Herrmann et al 2022[76]	RCC	Nivolumab	SMI (cm^2/m^2), BMI (kg/m^2)	OS, PFS	Median BMI >26, +weight gain associated with longer OS
Martini et al 2020[75]	Melanoma, GI, Lung, Head and Neck, Breast, Other	Immunotherapy-based phase I clinical trials	BMI (kg/m^2); SFI, IFI, VFI (cm^2/m^2)	OS, PFS	SFI ≥73, IFI <3.4, BMI >27 associated with longer OS
Martini et al 2021[74]	RCC	Anti-PD-1 monotherapy, ICI-combination regimen	SMI, SFI, IFI, VFI, TFI (cm^2/m^2)	OS, PFS, CB	BC-poor risk group had shorter OS, PFS, and decreased chance of CB
Ged et al 2022[77]	RCC	Anti-PD1 or Ant-PDL1, Anti-PD1 + Anti-CTLA4, Anti-PD1 + Anti-PDL1	BMI, SMI, multiple adiposity indexes	OS, PFS, ORR	High-BMI had longer OS vs. normal weight
Zahoor et al 2018[80]	RCC	Nivolumab	NLR	OS, PFS, RPD	Higher baseline NLR associated with increased risk of progression
Bilen et al 2018[79]	RCC	Nivolumab	NLR	OS, PFS	NLR >5.5 had median PFS 2.6 months and OS 2.7 months
Bilen et al 2020[78]	Melanoma, GI, Lung, Head and Neck, Breast (results not complete), Other	ICI + experimental combo, Anti-PDL1 monotherapy, Experimental IO	NLR, MLR, PLR; SMI; Combination Risk Grouping	OS, PFS	Low-risk (nonsarcopenic, PLR<242) had significantly longer OS, PFS
Aslan et al 2022[82]	RCC	ICI mono- and combo-therapy	SMI, NLR, Albumin	OS, PFS	CXI<median score had median OS of 7 vs. 48 months, and PFS of 4 vs. 17 months

TABLE 2 | Summary of studies using sarcopenic, inflammatory or nutritional parameters to predict ICI efficacy in advanced malignancies. Abbreviations: Non-small cell lung cancer (NSCLC), urothelial carcinoma (UC), mean skeletal muscle attenuation (MMA), gastrointestinal (GI), subcutaneous fat index (SFI), intermuscular fat index (IFI),visceral fat index (VFI), total fat index (TFI), clinical benefit (CB, defined as stable/improved radiographic disease at ≥6 months) body composition (BC), radiological progressive disease (RPD).

6.0-11.0]), OS at 24 months (79.2% vs 70.4%; hazard ratio [HR] for death, 0.66 [95% CI, 0.49-0.88]; p=0.005), and ORR (71.0% vs 36.1%; relative risk [RR], 1.97 [95% CI, 1.69-2.29]) versus sunitinib.

These immunotherapy regimens represent the approved, first-line and preferred options for the treatment of RCC, with many other immune-checkpoint inhibitor-based combinations or monotherapies currently under investigation or awaiting approval[12,34–38].

Interplay between ICIs and RCC

The tumorigenesis and development of RCC is well documented. Clear cell RCC frequently contains multiple loss-of-function mutations in the tumor suppressor gene Von Hippel-Lindau (VHL). This results in the induction of hypoxia inducible factors (HIF), which promotes cells to express VEGF and other factors that increase tumor angiogenesis and growth.[39] These findings were the basis for anti-angiogenic agents becoming the standard of care for advanced RCC. These drugs demonstrated improvements in OS and PFS, but without significant complete or durable response rates as monotherapies.[40]

It has become better documented how multiple subtypes of RCC share

alterations of specific pathways involving metabolism, hypoxia, and immune checkpoints.[41,42] RCC is notably associated with a highly inflammatory microenvironment with increased frequency of tumor infiltrating lymphocytes.[43] Despite prominent levels of T-cells within tumors, RCC often escapes via immunosuppressive mediators from the microenvironment or tumor cell overexpression of CTLA-4 and PD-L1 which block T-cell responses.[43] This infiltrate is partially composed of regulatory T cells (Treg), which can prevent cancer antigen recognition, and reduce the antitumor activity of lymphocytes present.[44] Markers associated with T-cell exhaustion along with the promotion of Th2 induction have been identified, which can allow for unchecked tumor growth in a state of chronic inflammation.[41,45] These findings support the use and improved benefits associated with immunotherapy in the treatment of RCC. However, many patients may not respond to immunotherapy and durable responses remain an exception, which can reflect the presence of primary and secondary resistance to ICIs.

There are multiple theories that explain resistance including certain patient-intrinsic, tumor cell-intrinsic, and tumor microenvironment factors.[46] One explanation is the tumor cell-induced release of VEGF which promotes abnormal neovascularization, Treg proliferation, and reduces CD8+ T-cell proliferation and penetration into the tumor. This supports the rationale for combining ICIs and anti-VEGFR TKIs as dual therapy for mRCC to target both antitumor processes.[40,47] Other explanations for potential ICI resistance include Wnt/ß-catenin pathway overexpression leading to T-cell exclusion and resistance to anti-PD(L1) and CTLA-4 antibodies along with MAP Kinase alterations that inhibit T-cell recruitment and function.[46] For patients that do respond to ICIs there is often a robust activation of CD8+ T-cells within the microenvironment, along with increased interferon-gamma signaling that promotes acute inflammation.[48] However, over time, evidence suggests an adaptation to increased T-cell checkpoint molecule expression that can lead to immunotherapy resistance.[48] Patient-specific factors, including sarcopenia, systemic inflammation and markers of nutritional status, remain an important barrier to immunotherapy efficacy and can be identified and addressed for improved management of advanced RCC.

SARCOPENIA, INFLAMMATION, AND MALNUTRITION IN ADVANCED RENAL CELL CARCINOMA

Definitions, Epidemiology, Relationships, and Pathophysiology

Sarcopenia is a generalized skeletal muscle disorder defined by 3 main criteria: low levels of muscle strength, muscle quantity and/or quality, and decreased physical performance which can indicate severity.[13,49] Cross-sectional imaging with computed tomography (CT) or magnetic resonance imaging (MRI) is widely prevalent during RCC screening, staging, and follow-up and can additionally be used to evaluate for sarcopenia at the third lumbar vertebra (L3), which correlates well with total skeletal muscle mass.[50–53] Commonly, the skeletal muscle index (SMI, cm2/m2) is calculated by dividing cross-sectional area of skeletal muscle at L3 by the patient's height in meters squared.[54] Then, SMI thresholds are used to define sarcopenia vs. nonsarcopenia; however, it should be noted that there is wide variation in SMI thresholds used to define sarcopenia, which is an important consideration for future incorporation and study interpretation.[55]

There has been further investigation since sarcopenia was first defined to clarify specific categories including primary and secondary forms, acute and chronic sarcopenia, sarcopenic obesity, and malnutrition-associated sarcopenia.[49] Primary sarcopenia refers to age-related changes, where, in addition to hormonal, physical activity, and nutritional changes, a state of chronic low-grade inflammation can contribute to the loss of muscle over time.[49,56] Based on established thresholds for muscle mass, up to 20% of those aged 70-79 and 30% of the population 80 or older meets this criterion for sarcopenia.[57] In addition, studies have demonstrated a high prevalence of weak muscle strength and decreased physical performance in populations aged 65 or older, affecting up to half of all individuals.[57]

Normal aging is associated with elevated levels of pro-inflammatory markers, including tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP), often associated with long-standing mitochondrial and immune dysfunction, cellular injury, and increased adiposity.[58] Multiple studies have demonstrated that higher levels of circulating cytokines, including TNF-α and IL-6, are associated with loss of skeletal muscle mass and strength, with an overall increased risk of sarcopenia.[59–61] In a separate meta-analysis, CRP is suggested to be a potential parameter for detecting sarcopenia given its association with higher serum levels in sarcopenic patients.[62] Alterations in pro-inflammatory markers can, directly and indirectly, affect skeletal muscle metabolism by increasing catabolic pathways for muscle breakdown, and preventing appropriate use of proteins for muscle synthesis.[56]

Systemic inflammation is also associated with solid malignancies and can exacerbate typical age-related skeletal muscle mass loss and contribute to worse outcomes. In a meta-analysis of over 80,000 patients with malignant tumors, sarcopenia was identified in 35.3%, and varied between 35-50% in RCC.15 Cancer

and its treatments can increase the risk of developing sarcopenia via the promotion of anorexia, physical inactivity, and pro-inflammatory states, along with treatment related damage to muscle tissue.[63] The development of sarcopenia can also co-occur as a component of cancer cachexia, defined as a progressive, multifactorial syndrome with continuous loss of skeletal muscle mass resulting in functional impairment that cannot be fully reversed.[16] Cancer cachexia arises from a combination of systemic inflammation and negative energy balance and affects ~30% of all cancer patients and close to 80% of patients with metastatic disease to the brain.[64] The diagnosis requires certain changes in overall weight, BMI, and sarcopenic criteria.[16] Furthermore, advanced cancer patients are often affected by nutritional impact symptoms, including anorexia, nausea, vomiting, taste, and smell changes, as a result of chemotherapy, radiotherapy, and even systemic inflammation that can alter hunger/satiety signaling thus preventing compensation for the ongoing negative energy balance.[64]

General Impact of Sarcopenia, Inflammation and Malnutrition on Survival in RCC

Sarcopenia is associated with poor OS and CSS across a wide variety of non-hematological solid tumors.[65] In a systematic review examining treatment-related outcomes for patients undergoing nephrectomy for localized and mRCC, sarcopenia was an independent predictor of mortality, especially following systemic treatment.[66] In patients with non-mRCC treated with radical nephrectomy, Psutka *et al* found sarcopenia as inferior 5-year CSS (79% vs 85%, p=0.05) as well as inferior 5-year OS (65% vs 74%, p=0.005).[19] In a study of mRCC patients, sarcopenia was associated with a 2.5x higher risk of all-cause mortality. and improved the prognostic ability of the MSKCC risk model when included with or substituted for Karnofsky performance status.[21] Similar results have been found in other cohorts of patients with metastatic and nonmetastatic RCC.[18,67]

Increasingly, sarcopenia with other markers of inflammation and nutrition are being considered and have demonstrated an association with increased mortality.[17,18,20,68] Higher modified Glasgow prognostic scores (mGPS), which features CRP and albumin as measures of inflammation and nutrition, have been associated with worse OS, CSS, RFS, and PFS, and have an even greater association when combined with sarcopenia.[18,29,69] Other studies have analyzed the predictive impact of the prognostic nutritional index (PNI) in patients undergoing nephrectomy, as calculated by albumin and lymphocyte levels.[26] Increases in PNI scores have shown a decreased risk of death from RCC.[25] PNI also demonstrated greater prognostic ability for both OS and PFS when compared to other inflammatory measures, such as Neutrophil-to-Lymphocyte (NLR), Platelet-to-Lymphocyte (PLR), and Lymphocyte-to-Monocyte (LMR) ratios.[25,26] On univariate analysis, these indices were associated with shorter OS and PFS, but only PNI was significant on multivariable analysis.[26] Multiple methods of evaluating for sarcopenia, inflammation, and nutritional status exist and demonstrate prognostic utility in localized and advanced RCC.

IMPACT OF SARCOPENIA, MALNUTRITION, AND INFLAMMATION ON IMMUNE CHECKPOINT EFFICACY

Examination of ICI efficacy and toxicity in relation to sarcopenia and other markers of nutrition and inflammation has emerged over the past decade. A representative summary of studies examining these interactions is summarized in **Table 2**.

Sarcopenia

A retrospective analysis of patients with advanced cancer receiving ICIs found sarcopenic patients experienced worse ORR (15.9% vs 30.5%, p=0.095) although this was statistically insignificant.70 However, 1-year PFS (10.8% vs 32%; RR, 1.31; p<0.001) and OS (43% vs 66%; RR 1.71; p<0.001) were significantly lower for the sarcopenic patients.[70] In another group of patients with advanced solid tumors that received ICI monotherapy, sarcopenia prevalence was nearly 50% and a significant predictor of worse OS, PFS, and ORR and not dependent on the type of ICI received.[71]

In addition to baseline muscle measurements, longitudinal change during ICI therapy has additionally exhibited prognostic ability. In one prospective study, [88] patients received either nivolumab (55.7%), pembrolizumab (28.4%), or nivolumab plus ipilimumab (9.1%) for various solid organ malignancies.[72] Although no difference in baseline SMI between responders vs. non-responders was observed, patients that responded to ICI therapy at the 3-month mark experienced an increase in SMI (+1.73 vs -3.20 mm2/cm, p=0.002) and median muscle attenuation (+0.89 vs -1.0 HU, p=0.090), an indicator of muscular fat deposition.72 Furthermore, OS was significantly lower (127 vs 547 days, p<0.001) in patients that experienced a strong decline in SMI (<-6.18 mm2/cm) or muscle attenuation (<-0.4 HU) compared to patients with stable or mild decreases.[72] The progressive loss of muscle mass with increased myosteatosis might reflect increased malignancy-associated inflammation which may negatively influence the antitumor effects of ICIs.[73]

Alternative Body Composition Parameters

In addition to quantified muscle composition, other parameters such as BMI, adipose distribution, and muscle quality may be informative. In an analysis of 79 patients treated with ICI for mRCC, Martini *et al* measured density (as measured via HU) of skeletal muscle, subcutaneous fat, intramuscular fat, and visceral

fat in addition to SMI. Patients were stratified into poor, intermediate, or favorable risk groups based on these measurements, with the poor risk groups experiencing significantly shorter OS, PFS, and lower chance of radiographic response at 6 months compared to the favorable risk group.[74] Furthermore, a lower total fat index was also associated with shorter OS, PFS, and a lower chance of radiographic response.[74] These findings suggest that, in addition to muscle quantification, markers of adiposity and muscle quality (i.e. intramuscular fat) may be informative and predict outcomes for patients with RCC receiving ICI therapy. This aligns with prior studies demonstrating that increased BMI, weight gain, increased subcutaneous fat index, and decreased intermuscular fat index during ICI treatment are associated with prolonged survival or treatment response in patients with cancer,[75] including mRCC.[76,77]

Inflammation

Relationships between inflammation and body composition in patients receiving ICI have also been considered. In 90 patients enrolled in immunotherapy-based phase 1 clinical trials, Bilen et al. risk-stratified patients based on sarcopenia measurements and baseline inflammatory markers (i.e. NLR, MLR, and PLR). A negative correlation was observed between SMI and PLR, and very high-risk (PLR ≥242 and sarcopenic) or intermediate (PLR <242 and sarcopenic) risk groups experienced significantly shorter OS and PFS compared with low-risk patients (PLR <242 and non-sarcopenic).[78] In a separate study of 38 mRCC patients treated with nivolumab, Bilen et al demonstrated that low NLR values were associated with longer median PFS (not estimable vs 2.6 months; HR 0.20 [95% CI, 0.07-0.64; p=0.006]) and OS (not estimable vs 2.7 months; HR 0.06 [95% CI, 0.01-0.55; p=0.012]).[79] These findings were echoed by Zahoor et al, where a higher baseline NLR was associated with an increased risk of progression in mRCC patients treated with nivolumab.[80] It is well documented how both inflammation and sarcopenia contribute to worse outcomes in malignancy and can limit treatment efficacy, but the inclusion of multiple markers for risk stratification may better account for multiple underlying prognostic factors.

Nutritional Status

Advanced RCC patients are often susceptible to malnutrition and resulting cancer cachexia, which can affect ICI efficacy. As previously discussed, higher PNI is associated with better survival. In a series of studies from Asian countries looking at PNI and survival outcomes in advanced cancer patients treated with ICIs, higher PNI was associated with greater ORR and longer OS and PFS.[81] The cachexia index is another combined score of sarcopenic and inflammatory markers used as a prognostic model in cancer patients. This index, based on SMI, NLR, and albumin levels, was used in a retrospective review of 52 mRCC patients who had received ICI as a 2nd-line or later treatment.[82] Below median cachexia index score was found to significantly affect OS (7 vs 48 months; HR 4.5 [95% CI, 1.9-11; p=0.001]) and PFS (4 months vs. 17 months; HR 2.6 [95% CI, 1.3-5.3; p=0.007]) as opposed to the other markers.82 One theory for why the procatabolic and proinflammatory state associated with cancer cachexia may interfere with ICI efficacy is increased clearance and metabolism. A prospective cohort study on the pharmacokinetics of nivolumab used in advanced cancers, including 14 patients (6.3%) with mRCC, showed how increased body-surface area and decreased albumin were associated with increased clearance of the ICI.[83] A clearance-response trend was observed in mRCC where clearance was higher in patients with progressive disease, although this was non-significant.83 However, this trend was significant in NSCLC (n=158; 71.5%), and given the smaller percentage of patients with mRCC, the study may have been underpowered to demonstrate statistical significance in this subgroup.

IMMUNE CHECKPOINT INHIBITOR TOLERANCE

In a series of 8 studies that featured patients with advanced RCC and other metastatic solid tumors, no association between patients with sarcopenia and adverse reactions of any grade were identified.[84] However, in a separate review, an increased risk of AEs with the use of ICIs in sarcopenic cancer patients was observed.[85] In addition to standard TRAEs from systemic therapy, numerous immune-related adverse events (irAE) associated with ICI use that result from upregulation of the host immune system.[86] The most commonly affected organs include the gastrointestinal tract, endocrine glands, skin, and liver.[86] Intriguingly, in a review of 90 patients with ICI-treated RCC, there was a 42% prevalence of irAEs, and this cohort demonstrated improved OS compared to patients without irAEs (35.9 [95% CI, 24.3 to non-estimable] vs 26.5 months [95% CI, 10.2-28.8]; p=0.002).[87] Similar studies have supported the findings of longer OS and PFS in ICI-treated RCC patients reporting greater irAEs.[88,89] In a meta-analysis of patients with advanced solid tumors, researchers analyzed sarcopenia in relation to irAEs, but the findings were mixed: two of the studies found no significant association between sarcopenia and irAEs, however, the 3rd study did identify a higher chance of developing irAEs in the sarcopenic group.[85] An association between sarcopenia and grade 3-4 irAEs may explain the lack of survival benefit in this cohort compared to other studies assessing the prognostic value of irAEs.[90] Although certain studies support sarcopenia as a risk factor for ICI TRAEs, the topic remains controversial and study-dependent. From a pharmacokinetic perspective, susceptibility to TRAEs in sarcopenic patients

makes sense; however, much of the research is limited by sample size, retrospective nature, and inclusion of a wide diversity of tumor types. New prospective studies should be pursued to examine the impact that muscle, inflammation, and nutrition may have ICI-related toxicity in RCC.

CONCLUSIONS

There remains a high prevalence of RCC cases that are either diagnosed at or progress to an advanced stage. ICI-based regimens including ICIs have emerged as first-line treatments for patients with advanced or metastatic disease. Measurements of sarcopenia, inflammation and nutrition hold potential prognostic value for the long-term outcomes of localized and advanced RCC. Strategies aimed for preventing and managing sarcopenia may have significant impact on improving outcomes and quality of life in patients with metastatic RCC.

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