

Evolving Paradigms in the Management and Outcomes of Sarcomatoid Renal Cell Carcinoma in the Era of Immune Checkpoint Inhibitors

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Abstract

Renal cell carcinoma (RCC) is a common cancer that affects a significant number of patients every year around the world. The presence of sarcomatoid features in these tumors is considered a poor prognostic feature. Patients with RCC with sarcomatoid features had significantly worse outcomes when treated with sunitinib, the previous first-line standard of care therapy when compared to patients without such features. Multiple immune checkpoint inhibitors have recently been approved for the treatment of RCC. In this article, we review the literature available on the outcomes of patients with sarcomatoid RCC treated with immune checkpoint inhibitors.

Keywords: Sarcomatoid; Renal cell carcinoma; Immune checkpoint inhibitors; Sunitinib

Introduction

The American Cancer Society estimates about 73,750 new cases of kidney and renal pelvis cancers, with about 14,830 deaths in the United States of America in 2020 [1]. Globally, these

constitute 2.2% (403,262) of all new cancer cases with almost 1.8% (175,098) deaths associated with them [2]. The median age of onset for this disease is around 64 years, affecting males almost twice as frequently as females [1, 2]. There are different histopathological variants of renal cell carcinoma (RCC), which constitutes the majority of kidney cancers. The most common type is the clear cell renal cell carcinoma (ccRCC), constituting about 70-75% of all cases. It is followed by papillary (10-15%), chromophobe (5%), collecting duct renal cell carcinomas (1%) and medullary carcinoma (1%) [3-5]. Sarcomatoid renal cell carcinoma (sRCC), which was previously considered a separate histological variant, is now regarded as a dedifferentiated carcinoma and can be associated with any RCC subtype [6]. The main feature of sarcomatoid type is the presence of pleomorphic spindle cells on the histopathological examination, which might also include rhabdoid, leiomyomatous, or fibrous components [6, 7] and American Joint Committee on Cancer (AJCC) (2017) staging has included these as histological grade 4 features. This sarcomatoid dedifferentiation can be seen in about 1-10% of RCCs and is associated with more aggressive and relatively poor clinical outcomes [8-10].

The prognosis in advanced RCC has been defined using International mRCC Database Consortium (IMDC) and Memorial Sloan Kettering Cancer Center (MSKCC) or Motzer score. These are based on quantification of number of risk factors individually associated with poor prognosis in RCC patients: Karnofsky score < 80%, < 12 months from diagnosis to systemic treatment, anemia, neutropenia, thrombocytosis, hypercalcemia and elevated lactate dehydrogenase. The median overall survival (OS) in advanced RCC treated with sunitinib in pre-immunotherapy era is reported as about 43.2 to 97 months, 22.5 to 33.5 months and 5.1 to 10 months in respective IMDC favorable (no risk factors), intermediate (1 - 2 risk factors) and poor risk groups (three or more risk factors) [11-14]. The prognostic impact of sarcomatoid features has also been reported in multiple retrospective studies. Kyriakopoulos et al looked at the outcomes of 2,286 patients with RCC, of which 230 patients had sRCC subtype. The average duration between the initial diagnosis and relapse was 18.8 months among sRCC, which was significantly shorter than 42.9 months reported in non-sRCC patients [9]. Similar findings were reported by Mian et al, which reported that 77% of sRCC had already metastasized at the initial presentation, and

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Table 1. Four Clinical Phase III Randomized Controlled Trials That Compared ICIs to Sunitinib

	Checkmate 214	IMmotion 151	KEYNOTE 426	JAVELIN renal 101
Drugs compared	Ipilimumab/nivolumab vs. sunitinib	Atezolizumab/bevacizumab vs. sunitinib	Axitinib/pembrolizumab vs. sunitinib	Axitinib/avelumab vs. sunitinib
N	60 vs. 52	68 vs. 74	51 vs. 54	47 vs. 61
ORR, %	56.7 vs. 19.2	49 vs. 14	58.8 vs. 31.5	46.8 vs. 21.3
CR, %	18.3 vs. 0	10 vs. 3	NR	NR
PFS, months	8.4 vs. 4.9	8.3 vs. 5.3	NR	7.4 vs. 4.0
OS	Median OS: 31.2 vs. 13.6 months	Median OS: 21.7 vs. 15.4 months	12 months OS: 83.4% vs. 79.5%	12 months OS: 83% vs. 67%

N: number of subjects with sRCC; ORR: objective response rate; CR: complete response rate; PFS: progression-free survival; OS: overall survival; NR: not reported; ICI: immune checkpoint inhibitor; sRCC: sarcomatoid renal cell carcinoma.

the median OS was about 8.5 months in these patients [15]. Sarcomatoid features along with larger tumor size (T3-4) have also been significantly associated with lymph node invasion at the time of radical nephrectomy. Among patients with localized RCCs undergoing nephrectomy with no residual disease but noted to have sarcomatoid features on pathology, 77% experienced recurrence with a median OS of only 2 years [16].

Immune checkpoint inhibitors (ICIs) have recently changed the treatment landscape of RCCs. These drugs are the monoclonal antibodies which target programmed death 1 (PD1)/programmed death ligand 1 (PDL1) and cytotoxic T-lymphocyte antigen 4 (CTLA-4) pathways, which are normally upregulated to protect normal tissues from excessive inflammation by inhibiting T-cell activation but also used by cancer cells to escape T-cell mediated anti-tumor immune responses [17]. For example, CTLA-4 is upregulated on the T cells in feedback to T-cell receptor (TCR) stimulation and engagement. It attenuates the TCR signaling by competing with the costimulatory molecule CD28 for the B7 ligands on the antigen presenting cells (APCs). CTLA-4 has higher affinity for the B7 ligands compared to CD28, thus effectively attenuating T-cell activation. Thus, tumor infiltrating APCs are better able to engage T cells in presence of CTLA-4 blockade. PD1 is also expressed on the T cells upon activation and PDL1 is expressed on APCs in response to interferon-gamma (IFN- γ) and on the cancer cells. PD1/PDL1 engagement inhibits T-cell activation via tyrosine phosphatase (SHP2)-based de-phosphorylation of activating signaling molecules in the T cells [18-21]. Some of the factors and biomarkers that have been shown and are being studied to predict a response to ICIs include tumor PDL1 expression, tumor immunogenicity and lymphocytic infiltration, tumor mutational burden (TMB) and deficiency in DNA mismatch repair genes (dMMR). Although dMMR and TMB ≥ 10 mutations/megabase have been approved by FDA as indications for use of pembrolizumab in unresectable or metastatic solid tumors irrespective of tumor site, but the only marker that has the strongest evidence towards predicting the response to all the different ICIs has been the PDL1 expression. The reliability of PDL1 as a predictive biomarker has been more consistent at its higher expression levels compared to lower expression levels and thus the quest to find a better predictive biomarker still continues. sRCC tumors have been reported to elicit significantly higher PDL1, PD1 and CD8 positive lymphocyte density in comparison to non-sarcomatoid

grade 4 ccRCC. Joseph et al reported higher PD1 positive tumor infiltrating lymphocytes (96% versus 62%) and higher PDL1 expression (54% versus 17%) in sRCC compared to ccRCC [22-24]. These findings are exciting for sRCC which historically has poor responses to the anti-angiogenic therapies.

Multiple ICIs (PDL1 inhibitors: atezolizumab, avelumab and durvalumab; PD1 inhibitors: nivolumab, pembrolizumab and cemiplimab; CTLA-4 inhibitors: ipilimumab) have been developed and FDA approved for numerous indications [25, 26]. In advanced RCC, ICIs are currently approved as monotherapy (nivolumab), in combination (nivolumab plus ipilimumab) and along with tyrosine kinase inhibitors (TKIs) (avelumab/pembrolizumab plus axitinib) at different lines of treatment. We have reviewed the literature and current evidence on the role of ICI in the treatment of sRCC (RCC with sarcomatoid dedifferentiation), which historically has had poor outcomes with TKIs monotherapy [27].

Review

Five recent clinical trials have studied the efficacy of multiple ICIs either as a single agent, in combination with a second ICI, or in combination with a vascular endothelial growth factor (VEGF) inhibitor in the treatment of advanced RCC. Four of these trials (Table 1) were phase III randomized controlled trials that compared ICIs to sunitinib (standard of care at the time of enrollment). These trials enrolled patients with advanced RCC who were treatment-naive.

Checkmate 214

Checkmate 214 is a phase III randomized open-label study comparing the efficacy of nivolumab plus ipilimumab vs. sunitinib among patients with untreated advanced or metastatic RCC. Patients were treated with nivolumab plus ipilimumab intravenously every 21 days for four doses, followed by nivolumab every 14 days, or sunitinib (50 mg) orally once daily for 4 weeks (6-week cycle). The objective response rate (ORR) was significantly higher (42% versus 27%) in the combination arm. At 18 months, 75% of the patients were alive in nivolumab/ip-

ipilimumab combination arm compared to 60% in sunitinib arm (hazard ratio (HR) for death was 0.63, $P < 0.001$) [28]. A *post hoc* analysis of this study for patients with sarcomatoid RCC subset identified 112 patients with sRCC, of which 60 patients were randomized to the nivolumab/ipilimumab arm and 52 to the sunitinib arm. The ORR was 56.7% in patients who received nivolumab/ipilimumab compared to only 19.2% in the sunitinib arm. The complete response rate (CR) was 18.3% in nivolumab/ipilimumab arm and 0% in the sunitinib arm. Patients in the combination arm had significantly higher OS and median progression-free survival (PFS) [29]. The combination is currently recommended as first-line treatment for patients with clear cell RCC who are classified as IMDC poor or intermediate risk by the National Comprehensive Cancer Network.

KEYNOTE 426

This is a phase III randomized open-label study that compared the efficacy of pembrolizumab plus axitinib for the treatment of advanced, previously untreated RCC in comparison to sunitinib monotherapy. A total of 861 patients underwent randomization, with 432 patients assigned to the combination arm, and 429 patients assigned to the sunitinib arm. The ORR was 59.3% in the pembrolizumab-axitinib group and 35.7% in the sunitinib group with a CR of 5.8% of patients in the pembrolizumab-axitinib group and 1.9% in the sunitinib group. On subgroup analysis presented at the ASCO 2019 meeting, out of the 861 patients enrolled in the trial, 105 had RCC with sarcomatoid dedifferentiation, of which 51 patients were randomized to pembrolizumab plus axitinib arm and 54 to the sunitinib arm. Pembrolizumab plus axitinib arm was reported to have a higher OS of 58.8% compared to 31.5% in the sunitinib arm. PFS and OS were favorable with ICI-combination arm, but the difference did not meet statistical significance (PFS HR 0.54, 95% confidence interval (CI) 0.29 - 1.00; OS HR 0.58, 95% CI 0.21 - 1.59). This clinical trial has led to the approval of pembrolizumab plus axitinib as a first-line treatment of advanced clear cell RCC in all IMDC risk categories [30].

KEYNOTE 427

This is a phase II single-arm open-label monotherapy clinical trial on the use of pembrolizumab for locally advanced/metastatic RCC. The study has two cohorts: cohort A included patients with clear cell RCC, with a total number of 110 patients, and cohort B included patients with non-clear cell RCC with a total number of 165 patients. Cohort A included 11 patients with sarcomatoid features, and these patients had an ORR of 64% with a disease control rate of 73% [31]. Cohort B included 38 patients with sarcomatoid RCC, with an analysis of this subgroup revealing an ORR of 44.7% [32].

IMmotion 151

This is a phase III open-label randomized controlled trial that

compared atezolizumab (1,200 mg) plus bevacizumab (15 mg/kg) every 3 weeks to sunitinib (50 mg daily for 4 weeks on/2 weeks off) in patients with treatment-naïve unresectable locally advanced or metastatic RCC with any component of clear cell or sarcomatoid histology. A total of 915 patients participated in the study, 454 patients were randomly assigned to the atezolizumab plus bevacizumab arm, and 461 patients were assigned to the sunitinib arm. Out of the 915 patients enrolled, 142 had sarcomatoid histology, 68 of these patients were assigned to the atezolizumab/bevacizumab arm, and 74 were assigned to the sunitinib arm. The study noted that patients with sarcomatoid histology have higher expression of PDL1 (with 61% expressing PDL1) and more likely to have intermediate to poor-risk disease. The data analysis of this subgroup showed a higher ORR in the atezolizumab/bevacizumab arm at 49% vs. 14% in the sunitinib arm. The CR was higher in the combination arm 10% vs. only 3% in the sunitinib arm. The median PFS for sarcomatoid histology was 8.3 months in the atezolizumab/bevacizumab arm compared to 5.3 months in the sunitinib arm. The HR for PFS was 0.46 (95% CI 0.28 - 0.78) in the PDL1 positive and 0.56 (0.38 - 0.83) in the intention-to-treat group. The median OS for sarcomatoid histology was not reported (18.3 months to NA) in the combination arm versus 15 months (8.7 to NA) in sunitinib arm, with HR of 0.56 (95% CI 0.32 - 0.96). The study concluded that patients with sarcomatoid histology treated with atezolizumab/bevacizumab had significantly longer PFS and OS [33].

JAVELIN renal 101

This is a phase III open-label randomized clinical trial comparing avelumab (10 mg/kg every 2 weeks) plus axitinib (5 mg orally twice daily) or sunitinib (50 mg orally once daily for 28 days on/14 days off) in the treatment of patients with previously untreated patients with advanced RCC. The trial enrolled a total of 886 patients, 442 patients received avelumab plus axitinib, and 444 patients received sunitinib. Of the patients, 63.2% had PDL1 positive tumors. The ORR was 55.2% with avelumab plus axitinib and 25.5% with sunitinib. The subgroup data analysis presented at European Society for Medical Oncology (ESMO) (2019) showed that out of the total enrolled subjects, 108 patients had sarcomatoid RCC, 47 patients received avelumab plus axitinib, and 61 patients received sunitinib. Of these patients, 90% had undergone prior nephrectomy; 72% in the combination arm and 85% in sunitinib arm were PDL1 positive. The ICI/TKI combination arm was reported to have an ORR of 46.8% compared to 21.3% in the sunitinib group. A CR was reported among two patients in the combination arm compared to none with sunitinib. Median PFS was prolonged in combination arm with HR of 0.57 (95% CI 0.325 - 1.003) [34].

Conclusions

sRCC is an aggressive form of RCC that can be associated with any histological subtype of RCC, but most commonly

seen with clear cell RCC. It is thought to be present in up to 20% of patients with advanced disease, with the majority of cases having intermediate or poor prognostic factors. Notable features of sRCC are the higher expression of PDL1, and the poor outcomes compared to clear cell RCC when treated with sunitinib. In all the mentioned clinical trials, patients with sRCC had statistically significant higher ORR, PFS, OS and CR when treated with ICIs compared to the previous standard of care monotherapy with sunitinib.

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None to declare.

Conflict of Interest

None to declare.

Author Contributions

Ragia Aly: manuscript idea, research, writing. Amandeep Aujla: writing, editing. Sachin Gupta: review, editing. Ruby Gupta: revision, editing. Sorab Gupta: revision, editing. Sheila Khalathil: editing.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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