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Long-term follow-up results of patients with sarcomatoid RCC: A retrospective evaluation of a single center experience

Sarkomatoid RHK tanılı hastaların uzun dönemli takip sonuçları: Tek merkez deneyiminin retrospektif değerlendirmesi

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Ethics Committee Approval: University of Health Sciences Dr. Abdurrahman Yurtaslan Ankara Oncology Health Practice and Research Center Clinical Research Ethics Committee (No: 220-08/755, Date: 8/26/2020). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
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Abstract

Aim: Sarcomatoid renal cell cancer (sRCC) is an extremely rare condition, and literature on disease management is limited. There are no treatment recommendations based on high-quality data. Our aim in this study is to reveal our long-term experience with patients diagnosed with sRCC.

Methods: Patients who were followed up with a diagnosis of sRCC between January 2010 and December 2019 were retrospectively evaluated in terms of main disease characteristics, treatments, treatment responses and survival times.

Results: Twenty-five (8.0%) of 311 RCC patients had sarcomatoid differentiation. The median age of the 25 patients included in the study was 58.1 (26.3-78.0) years, and the vast majority were male (n=18, 72%). Distant organ metastasis was present in 11 (44.0%) patients at the time of diagnosis. In 10 (71.4%) out of 14 patients who underwent curative surgery, recurrence was observed with distant organ metastasis. Thirteen (61.9%) of 21 metastatic patients received tyrosine kinase inhibitor (pazopanib or sunitinib) in second-line treatment. The progression-free survival for the second line treatment of these 13 patients was 6.1 months (95% CI: 3.8-8.4). Long-term disease control was achieved in one of the two patients who received nivolumab treatment. Cytoreductive nephrectomy was performed in seven (63.6%) of the 11 patients who were in metastatic stage at the time of diagnosis. Pulmonary metastasectomy was performed in two patients with lung metastasis. One of these two patients was still followed up without recurrence at the 112th month after metastasectomy. Overall survival was 10.8 months (85% CI: 8.9-12.6) for 21 patients in the metastatic stage.

Conclusion: sRCC is a rare disease with a poor prognosis. Systemic treatment efficacy is low with frequent distant metastases. Tyrosine kinase inhibitors are prominent among current treatment methods. Immune checkpoint inhibitors, one of the new generation treatment options, is promising in terms of treatment success. The addition of cytoreductive nephrectomy and metastasectomy to the treatment process may provide additional benefits.

Keywords: RCC, Sarcomatoid differentiation, sRCC, TKI, Nivolumab, Cytoreductive nephrectomy

Öz

Amaç: Sarkomatoid renal hücreli kanser (sRHK) oldukça nadir bir durum olup, hastalık yönetimi ile ilgili literatür verisi kısıtlıdır. Yüksek kalitede veriye dayanan tedavi önerileri yoktur. Bu çalışmadaki amacımız, sRHK tanılı hastalarımızdaki uzun süreli tecrübemizi ortaya koymaktır.

Yöntemler: sRHK tanısıyla Ocak 2010-Aralık 2019 arasında takip edilen hastalar, genel hastalık özellikleri, verilen tedaviler, tedavi yanıtları ve sağ kalım süreleri açısından retrospektif olarak değerlendirildi.

Bulgular: Üç yüz on bir RCC hastasının 25'inde (%8,0) sarkomatoid farklılaşma gözlendi. Çalışmaya dahil edilen 25 hastanın ortanca yaşları 58,1 (26,3-78,0)'di ve büyük çoğunluğu erkekti (n=18, 72%). Tanı anında 11 (%44,0) hastada uzak organ metastazı vardı. Küratif cerrahi yapılan 14 hastanın 10'unda (%71,4) uzak organ metastazı ile nüks izlendi. Metastatik 21 hastanın 13 (%61,9)'ü ikinci basamak tedavide tirozin kinaz inhibitörü (pazopanib veya sunitinib) aldı. Bu 13 hastanın ikinci basamak tedavisi için progresyonsuz sağ kalım süresi 6,1 aydı (%95 CI: 3,8-8,4). Nivolumab tedavisi alan 2 hastadan birinde uzun süreli hastalık kontrolü sağlandı. Tanı anında metastatik evrede olan 11 hastanın 7 (%63,6)'sinde sitoredüktif cerrahi uygulandı. Pulmoner metastazektomi yapılan 2 hastadan biri metastazektomi sonrası 112.ayda hala nükssüz izlenmekteydi. Metastatik evredeki toplam 21 hasta için genel sağ kalım süresi 10,8 aydı (%85 CI: 8,9-12,6).

Sonuç: Sarkomatoid RCC oldukça nadir görülen ve kötü prognoza sahip bir hastalıktır. Hastaların çoğunda uzak organ metastazı gözlenmekle birlikte sistemik tedavi etkinliği düşüktür. Güncel tedavi yöntemleri içinde tirozin kinaz inhibitörleri ön plandadır. Yeni nesil tedavi seçeneklerinden olan immun kontol noktası inhibitörleri tedavi başarısı açısından ümit vaat etmektedir. Sitoredüktif nefrektomi ve metastazektominin tedaviye eklenmesi ek faydalar sağlayabilir.

Anahtar kelimeler: RHK, Sarkomatoid diferansiyasyon, sRHK, TKİ, Nivolumab, Sitoredüktif nefrektomi

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Introduction

Sarcomatoid renal cell cancer (sRCC) is defined as the tumor exhibiting pronounced cytological atypia and containing malignant spindle cells resembling sarcoma [1]. Sarcomatoid differentiation may accompany many subtypes of RCC. It refers to a high-grade transformation rather than a different histological entity. In 2012, it was redefined as dedifferentiation characterized by the loss of epithelial features [2]. Although it varies according to histological subtypes, it is seen in approximately 5-8% in all RCCs [3,4]. However, when metastatic cases are considered, sarcomatoid differentiation can be seen in nearly 20% [5]. sRCC has a very aggressive clinical course, and stage IV cases are frequently encountered [3, 4]. In a study involving patients diagnosed with metastatic RCC, the overall survival (OS) was 22.2 months in patients without sarcomatoid differentiation. In contrast, it was 10.0 months in patients with sRCC [6]. Metastatic RCC treatment has improved significantly in recent years with targeted treatment options, but the effectiveness of these drugs against sRCC is limited [7]. Objective tumor response was detected with doxorubicin-gemcitabine combination chemotherapy to treat metastatic sRCC [8]. However, the results of phase II studies evaluating the effectiveness of chemotherapy on survival in the treatment of metastatic sRCC are inconsistent [9]. Since it is rare, it could not find enough place in extensive prospective studies in clinical course, treatment, and survival evaluations. Therefore, although the clinical features are different from conventional RCC, in international treatment guidelines, there are not enough additional recommendations for sRCC treatment [10,11]. Our current study aimed to share our experiences in sarcomatoid RCC, where clinical data are usually based on small or retrospective studies.

Materials and methods

The data of patients treated and followed up with the diagnosis of RCC between January 2010 and December 2019 in the medical oncology clinic of the University of Health Sciences Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital were retrospectively evaluated. Patients diagnosed with RCC with sarcomatoid differentiation were included in the study. Patients with insufficient data in terms of histopathological evaluation and medical records were excluded from the study. Patients who had a baseline visit but had no follow-up visits were excluded. Patients' demographic characteristics, stages at the time of diagnosis, surgical modalities, recurrence, metastatic sites, systemic treatments, systemic treatment response rates, progression-free survival (PFS), and OS times were evaluated, which were compared with the literature data. Local ethics committee approval was obtained, and the study was conducted in accordance with the principles of the Helsinki Declaration.

Statistical analysis

Descriptive statistics were used to show the distribution of the main characteristics of the population. PFS was defined as the time interval between the initiation of systemic treatment and progression. OS was defined as the time interval between histological diagnosis and time of death or last follow-up. Survival rates were estimated with the use of the Kaplan–Meier method. A comparison was made using the log-rank test to evaluate the difference in survival between groups. Analyses were performed using IBM SPSS Statistics version 24.0 software (SPSS Inc., Chicago, IL, USA).

Results

Sarcomatoid differentiation was observed in 25 (8.0%) of 311 RCC patients. The main patient and tumor characteristics in the study population of 25 patients with a median age of 58.1 (26.3-78.0) years and mostly males (n=18, 72%) are displayed in Table 1. The median follow-up period of the patients in the study was 13.7 (0.7-138.5) months.

Among the 25 patients included in the study, 14 (56%) patients who did not have distant metastases underwent curative surgery at the time of diagnosis. Cytoreductive nephrectomy was performed in 7 (63.6%) of 11 patients who were metastatic at the time of diagnosis. There were a total of 21 metastatic patients. Two of metastatic patients (9.5%) had lung metastasectomy. One of the patients was being followed up in remission at the 112th month after metastasectomy. While 3 (14.3%) of 21 metastatic patients could not receive any systemic treatment, 18 (85.7%) patients received various systemic therapies. Findings related to treatments are displayed in table 2.

Table 1: Patient and tumor characteristics (n=25)

Characteristic	Number	%
Age-Median (range)	58.1 (26.3-78.0)	
Gender		
Male	18	72.0
Female	7	28.0
Tumor Grade		
Grade II	8	32.0
Grade III	9	36.0
Unknown	8	32.0
Stage at Diagnosis		
Stage I	3	12.0
Stage III	9	36.0
Stage IV	13	52.0
Distant Metastasis at Diagnosis		
Yes	11	44.0
No	14	56.0
Recurrence *	10	71.4
All Metastatic Patients	21	84.0
Metastatic Sites **		
Lung	14	66.7
Bone	13	61.9
Lymph Node	6	28.6
Liver	4	19.0
Brain	1	4.8

* Calculated by proportioning to patients without distant metastases at diagnosis, ** Calculated by proportioning to all metastatic patients

Table 2: Treatment-related characteristics (n=25)

Characteristics	Number	%
Curative Surgery	14	56.0
Cytoreductive Nephrectomy *	7	63.6
Metastasectomy**	2	9.5
Systemic Treatments **		
First Line	18	85.7
Interferon	14	66.7
Pazopanib	1	4.8
Chemotherapy	3	14.3
Second Line	13	61.9
Pazopanib	10	47.6
Sunitinib	3	14.3
Third Line	4	19.1
Axitinib	2	9.5
Everolimus	1	4.8
Nivolumab	1	4.8
Fourth Line	1	4.8
Nivolumab	1	4.8
No systemic treatment	3	14.3

* Calculated by proportioning to patients with distant metastases at diagnosis, ** Calculated by proportioning to all metastatic patients

Three patients in the study received chemotherapy (1 patient gemcitabine, one patient gemcitabine-doxorubicin, one patient gemcitabine-docetaxel) as the first-line therapy. One patient who received chemotherapy developed SD after three cycles and PD after six cycles. At the same time, PD was observed after three cycles of chemotherapy in the other two patients. Three patients who received chemotherapy did not receive any treatment afterwards. Fourteen patients had received interferon-alpha (IFN) as first-line therapy. In 12 (85.7%) of 14 patients who received interferon, treatment could not be continued due to intolerance. The median time of IFN therapy in 12 patients with intolerance was 6 (1-38) days. Partial remission (PR) was achieved in 1 (50%) of the 2 patients who could tolerate IFN, and the duration of PFS with IFN for this patient was 13.0 months. The other 1 (50%) patient also developed PD at the first control in the 3rd month. Response rates to treatment agents are shown in Table 3.

The median OS was 19.7 months (95% CI: 9.9-29.6) when the entire patient group was considered. The median OS for patients at the metastatic stage was 10.8 months (95% CI: 8.9-12.6). The survival plot is displayed in Figure 1. Median OS was 10.8 months (95% CI: 9.8-11.7) for those who underwent cytoreductive nephrectomy and 8.7 months (95% CI: 0.0-18.0) for those who did not (P=0.493).

The median PFS was 6.1 months (95% CI: 3.8-8.4) for those who received tyrosine kinase inhibitor (TKI) (pazopanib or sunitinib) as second-line therapy, and the survival plot is displayed in Figure 2.

Table 3: Treatment response rates

Treatment Agent (n)	PR, n (%)	SD, n (%)	PD, n (%)
Chemotherapy (3)		1 (33.3%)	2 (66.7%)
Interferon (2)	1 (50.0%)		1 (50.0%)
Sunitinib (3)		2 (66.7%)	1 (33.3%)
Pazopanib (11)	2 (18.2%)	5 (45.4%)	4 (36.4%)
Axitinib (2)	1 (50.0%)		1 (50.0%)
Everolimus (1)			1 (100.0%)
Nivolumab (2)		1 (50.0%)	1 (50.0%)

PR: Partial Remission, SD: Stable Disease, PD: Progressive Disease

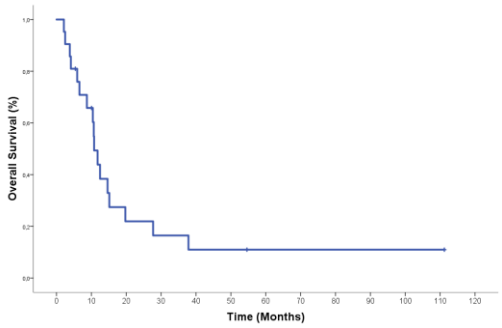

Figure 1: Overall survival for patients in the metastatic stage

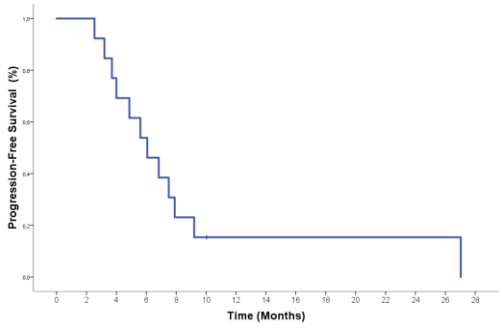

Figure 2: Progression-free survival for patients receiving tyrosine kinase inhibitors as second-line therapy

Discussion

In our current study, we shared our clinical experience in patients diagnosed with RCC with sarcomatoid differentiation. Sarcomatoid differentiation is not a common condition in RCC and is observed around 5-8% [3, 4]. In our study, we saw that 8% of the patients with RCC who were followed up in our clinic over 10 years had sarcomatoid differentiation. Albeit rare, it represents a major clinical challenge. It has been demonstrated to be an independent adverse prognostic factor for RCC [12, 13]. In a retrospective analysis involving sRCC patients who underwent curative surgery, 77% of distant metastases developed after approximately 26 months of follow-up [14]. In our study, the recurrence rate was 71.4% in patients who underwent curative surgery in accordance with the literature.

Systemic chemotherapy was considered one of the options that could provide efficacy in treating metastatic sRCC. Doxorubicin-gemcitabine combination therapy appears to be a relatively prominent option in this area. In the ECOG 8802 study, 16% of 39 patients who received doxorubicin-gemcitabine combination chemotherapy with a diagnosis of sRCC had an objective response, and 26% had stable disease. [8]. Nanus et al. reported CR in 2 and PR in 5 of 18 patients who received gemcitabine-doxorubicin [15]. Few patients in our study received gemcitabine-based chemotherapy as first-line therapy. However, all of them progressed, and none received second-line treatment due to deterioration in their performance status. Our study's poor chemotherapy outcomes and the inconsistent literature data [9] caused us to think negatively about chemotherapy.

In the first-line treatment of metastatic RCC, the primary current treatment options for clear cell histological subtype are anti-VEGF (vascular endothelial growth factor) TKI (sunitinib, pazopanib, tivozanib), anti-c-Met TKI (cabozantinib), anti-VEGF TKI and immune checkpoint inhibitor combination (axitinib-pembrolizumab), immune checkpoint inhibitor combination (nivolumab-ipilimumab) and anti-VEGF antibody and cytokine combination (bevacizumab-IFN) [10, 11]. There is no high-evidence recommendation for a different treatment option for patients with sarcomatoid differentiation in these guidelines. Although it is not recommended in international treatment guidelines according to Turkey's health insurance system's rules, to apply anti-VEGF TKI therapy, IFN must be used in first-line treatment. Therefore, most of our patients had received IFN treatment in first-line treatment. However, treatment could not be continued due to intolerance in most patients. One of the two patients who could continue with IFN therapy had an objective treatment response, and the other patient progressed. Treatment guideline recommendations and our findings led us to think negatively about the use of IFN.

There are robust data on anti-VEGF TKI, which forms the basis of metastatic RCC treatment. In a phase III study in patients with cytokine pretreated or treatment-naive metastatic RCC, a PFS of 9.2 months was achieved with pazopanib, significantly better than placebo [16]. In the long-term follow-up analysis, it was observed that OS was 22.9 months for these patients [17]. In the phase III study in which sunitinib's effectiveness was evaluated compared to IFN, PFS was significantly better in favor of sunitinib at five months versus 11 months [18]. Although sunitinib and pazopanib's significant

efficacy was demonstrated in these studies, sRCC is not included in subgroup analyses. In a retrospective analysis involving 230 sRCC patients, PFS (4.5 months vs. 7.8 months) and OS (10.4 months vs. 22.5 months) were significantly worse for sRCC compared to non-sRCC histological type [13]. Similar to this study, in our research, PFS was 6.1 months for patients who received pazopanib or sunitinib, and the OS was 10.8 months for patients in the metastatic stage. Although disease control (PR or SD) was achieved in approximately two-thirds of the patients with pazopanib and sunitinib in our study, survival times were significantly worse than patients' literature data without sarcomatoid differentiation. Our study results and literature data suggest that pazopanib and sunitinib can be beneficial in treating sRCC, but this may be limited.

In a randomized controlled trial, the non-inferiority of sunitinib treatment to sunitinib and cytoreductive nephrectomy was demonstrated [19]. However, the presence of an intense poor-risk group in this study makes it difficult to generalize the study results. Therefore, cytoreductive nephrectomy may be an option for patients with sRCC for whom systemic treatments are insufficient in terms of effectiveness. In a retrospective study evaluating cytoreductive nephrectomies performed for three decades, it was observed that the contribution of cytoreductive surgery to OS in patients with sRCC improved with chronological progress, but did not reach statistical significance. The same study could not clearly explain whether the improvement in survival contribution is due to cytoreductive nephrectomy or the advances in systemic treatments over time [20]. In our study, the OS of seven patients who underwent cytoreductive nephrectomy was approximately two months better, but it was not statistically significant. The low number of patients who underwent nephrectomy prevents us from making a definite interpretation. Another important point in terms of surgical treatments is metastasectomy. It has been stated that complete pulmonary metastasectomy may be beneficial in RCC patients with pulmonary metastasis [21]. In a study involving three patients with sRCC who underwent pulmonary metastasectomy, one patient's disease-free survival was seven months. It was stated that metastasectomy should be a component of the treatment of RCC patients with sarcomatoid differentiation [22]. One patient in our study who underwent pulmonary metastasectomy had no recurrence at the 112th month. Therefore, it should be kept in mind in all patients who are eligible for metastasectomy in the management of sRCC.

It has been determined that sRCC may express PD-1 / PDL-1 at a higher percentage compared to RCC without sarcomatoid differentiation [23]. It was stated in an earlier study that high PDL-1 expression is an independent factor associated with poor prognosis for RCC [24]. High PDL-1 expression may explain the poor prognosis of sRCC and indicate that immune checkpoint inhibitors will benefit in treating sRCC. A 53% ORR for sRCC was observed in a recent phase II study with atezolizumab-bevacizumab combination therapy [25]. Similarly, in the CheckMate 214 study, an exploratory analysis of sRCC cohort, an ORR of 56.7% was detected using a combination of ipilimumab-nivolumab [26]. Current immunotherapy options show promise in the treatment of sRCC. In our study, only two patients were able to receive nivolumab. Although one of them received treatment in the fourth line, stable response and survival of around 20 months were obtained. This time was longer than the total time for this patient on the 3-line treatment before nivolumab.

Limitations

The study's main limitations are its retrospective design and the small number of patients, although it was conducted in a rare patient group. Also, the percentage of sarcomatoid differentiation could not be obtained in pathological evaluation. Another limitation is the requirement to have used IFN before anti-VEGF TKI.

Conclusion

RCC with sarcomatoid differentiation shows a poor prognosis characterized by a high rate of recurrence and short survival. Current treatment options have limited efficacy in the treatment of sRCC. New generation immunotherapeutic drugs may contribute positively to survival. The addition of cytoreductive nephrectomy and metastasectomy to the treatment process may provide additional benefits. Prospective randomized studies are needed to optimize systemic therapies and surgical interventions in the management of sRCC.

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