Sarcomatoid renal-cell carcinoma: treatment strategy, review of the literature and a case report

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ABSTRACT

Introduction: Sarcomatoid renal-cell carcinoma is a very rare cancer characterised with aggressive course of disease and poor prognosis. At present there are no standards of care for this histologic subtype of renal cell carcinoma resistant to various forms of systemic treatment.

Methods: The study describes a case of 58 year old woman after left nephrectomy for clear cell carcinoma with sarcomatoid component and after resection of right-kidney tumour for synchronous clear cell carcinoma who received first-line bevacizumab and temsirolimus under the clinical trial, and then second-line chemotherapy based on gemcitabine and doxorubicin and ifosfamide-based third-line chemotherapy. The patient underwent pulmonary metastasectomy twice, and once a metastasectomy for liver metastases.

Conclusions: Surgery (including metastases treatment) followed by the systemic chemotherapy seems to be correct option of treatment in patients with renal cell carcinoma with sarcomatoid features. The development of optimum method of systemic treatment requires further prospective randomised trials.

KEY WORDS: sarcomatoid renal-cell carcinoma, chemotherapy, gemcitabine, doxorubicin, surgical treatment

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INTRODUCTION

Sarcomatoid renal-cell carcinoma is a rare and important cancer accounting for up to 5% of all renal-cell carcinoma subtypes. It is characterised with a very aggressive course of disease, rapid spread of cancer cells (mostly into lungs, bones, liver and lymph glands), short survival period (median survival rate 4–9 months), early recurrence of the disease after nephrectomy and high resistance to various forms of systemic treatment [1].

CASE REPORT

The study describes a case of 58 year old woman after left nephrectomy for clear cell carcinoma with sarcomatoid component in May 2009 and after resection of right-kidney tumour for synchronous clear cell carcinoma in August 2009. Due to the spread of the disease, in the first-line the simultaneous systemic therapy with bevacizumab and temsirolimus was introduced within the framework of clinical trial. It was permanently discontinued after 9 months due to the disease progression in the form of new lesions and the growth of already existing ones by 21.5% (October 2009–June 2010). The patient underwent two wedge lung resections for metastases and exploratory laparotomy due to abdominal metastatic lesions. During the laparotomy unresectable pancreatic tumor was confirmed, omentectomy and liver metastasectomy were performed. In the post-surgical histopathology of removed metastases the morphological blood picture and IHC profile confirmed undifferentiated pleomorphic sarcoma, CKEA 1-3 (-), CK 7 (-), CK 19 (-), CK 20 (-), VIM (+), CD 68 (+), HMB 45 (-), CD 117 (-), RCC (-) (fig. 1–3).

In October 2011 the patient attended the Oncology Clinic for the qualification to the next line of treatment due to disease progression. Based on Naomi et al. the decision was taken on the introduction of the next line of chemotherapy according to the programme based on doxorubicin and gemcitabine [2]. In total the patient received 9 chemotherapy courses. The best response to the introduced treatment was the reduction in lesions meeting the disease stabilisation criteria according to RECIST Version 1.1. Due to the toxicity of treatment appearing among the other as grade 3 neutropenia according to CTC-AE classification, following the 3rd course of chemotherapy the decision on dose reduction by 25% was taken. In April 2012 the patient was given the last – 9th course of chemotherapy.

In July 2012, due to disease progression the patient was qualified for the third-line chemotherapy with ifosfamide as monotherapy. Following the 1st course the toxicity of treatment was observed in the form of CTC-AE grade 2 anaemia which required red blood cell transfusion. Moreover the patient reported persistent constipation, nausea and vomiting. The introduced symptomatic treatment resulted in clinical improvement. The oncological treatment was discontinued after 2 courses due to the hematologic toxicity in the form of neutropenia, leukopenia, CTC-AE grade 4 thrombocytopenia and grade 3 anaemia.

FIGURE 1.
Sarcomatoid pattern of the cancer.

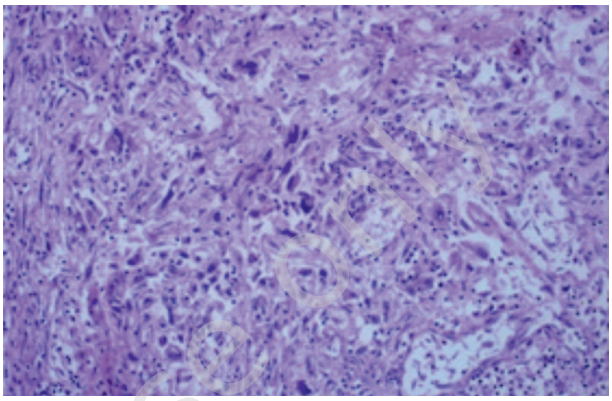


FIGURE 2.
Sarcomatoid pattern of the cancer, on the left – residual texture of the kidney with atrophic renal corpuscle.

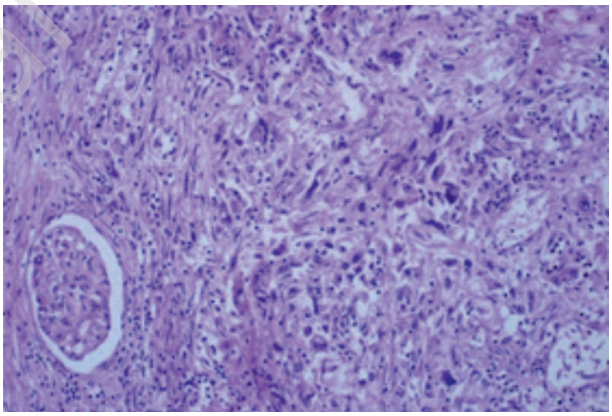
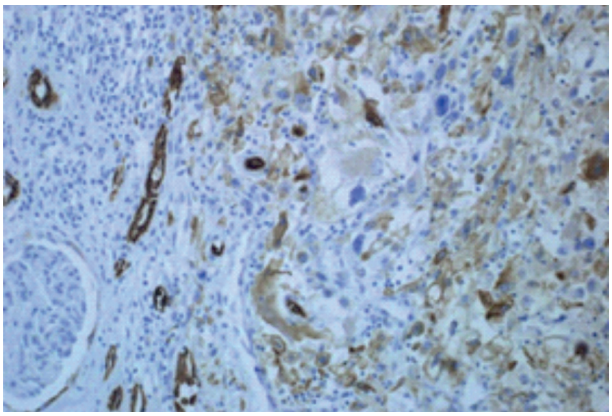


FIGURE 3.
Area shown in Picture 1 with staining for cytokeratin – positive response in the cancer pattern confirms the presence of epithelial cancer – carcinoma.



Further symptomatic treatment was recommended. The overall survival since diagnosis to date is 52 months.

DISCUSSION

Renal cell carcinoma accounts for about 3% of all tumours. It is more common in men than women (1,5 : 1), with a peak incidence between the ages of 60 and 70 years. The majority of cases are sporadic cancers; only about 5% of cases have genetic background as the part of hereditary syndromes, e.g. von Hippel-Lindau syndrome [7]. The clear-cell renal-cell carcinoma is the most common (80–90% of cases), and the sarcomatoid component is not a distinct histologic type but may be present with other renal-cell cancer types and according to various data is present in up to 5% of all renal-cell carcinomas. This malignancy often shows local invasion and distant metastases which translates to poor prognosis and short survival of these patients. Although the presence of sarcomatoid component may be the one of the most significant prognostic factors, the literature does not pay enough attention to this histologic subtype.

In the study conducted by Haas and WSP on 38 patients treated according to the aforementioned scheme median PFS and OS reached 3.5 months and 8.8 months respectively [2].

In an analysis of 18 patients conducted by Nanus et al. in 2004 some clinical responses with gemcitabine and doxorubicin combination therapy were reported. Among these patients, there were seen three responses including one complete response. The authors recently updated their experience with long-term survival of 4 patients with stage IV sarcomatoid renal cell carcinoma. The two complete responders are alive, disease free at 6 and 8 years after starting therapy, and the two patients rendered CR by surgery survived 3.5 and 6 years respectively [3, 9].

An analysis of Stachler et al. (2008) – evaluated sorafenib in 15 patients who had progression disease after gemcitabine and doxorubicin combination therapy. Median time to progression under this therapy was 6.6 month. During gemcitabine and doxorubicin treatment there were no remissions and 6 patients died from progressive disease. Median time to progression for patient switched to sorafenib was 10.9 months [4, 5].
Summary in table below.

The percentage share of sarcomatoid component in the renal tumour seems to be of significance. The conducted analyses have shown that better responses were observed in patients with the percentage of sarcomatoid pattern higher than 50% [8].
Summary of results in Table 2.

The alternative method of systemic treatment in this group of patients is the introduction of VGRF inhibitors with particular focus on sorafenib [4–6]. In a group of 43 patients, in 19% PR (9) in 49% SD (21), and in 33% (14) PD was achieved. Median PFS and OS was 5.3 and 11.8 months respectively [6]. The results were achieved in the group of patients where the sarcomatoid pattern was lower than 20% of the primary tumour.

TABLE 1.
Systemic therapy experience with sarcomatoid renal tumors. Own work based on [1].

Study	Treatment	Clinical trial	*n*	Response (CR/PR)	Objective response	%	PFS months	OS months
Nanus et al. (2004)	Gemcitabine + doxorubicin	No	18	2/5	7	39	5	N/A
Staehler et al. (2008)	Gemcitabine + doxorubicin	No	15	0/0	0	0.0	6.6	N/A
Haas et al. (2009)	Gemcitabine + doxorubicin	Yes	38	1/5	6	15.8	3.5	8.8

TABLE 2.
Responses of patients treated ECOG 8802 trial of doxorubicin and gemcitabine according to the percentage of sarcomatoid features by central review [2].

Best overall response	*N* (%)	≥ 75% sarcomatoid features	< 75% sarcomatoid features	Sarcomatoid features unknown
Complete response (CR)	1 (3)	1	0	0
Partial response (PR)	5 (13)	2	2	1
Stable disease (SD)[1]	10 (26)	3	2	5
Progression disease (PD)[2]	13 (35)	4	2	7
Unevaluable for response	9 (24)	1	2	6

Three of these four patients had pathology reviewed centrally.
[1] For at least 56 days. Includes 1 unconfirmed PR.
[2] Includes 4 patients with stable disease for 51–55 days.

There is ongoing clinical trial studying combination of gemcitabine with sunitynib in patients with sarcomatoid or poor-risk RCC. Several clinical factors have been described to identify patients with poor-risk disease. Motzer et al. initially characterized 5 risk factors as prognostic, and patients with 3 or more of these risk factors were defined as poor-risk [10]:

- decreased performance status
- elevated serum lactate dehydrogenase
- elevated serum calcium
- anemia
- absence of prior nephrectomy.

In group of 39 patients had sarcomatoid RCC ORR was 26%, and in group of 33 with poor-risk RCC ORR was 24%. The median TTP and OS for patients with sarcomatoid RCC were 5 and 10 months, respectively. For patients with poor-risk disease, the median TTP and OS were 5.5 and 15 months, respectively. Also in that trail percentage of sarcomatoid features in patients shows influence on clinical benefit rate (ORR plus stable disease). The results are promising in group where sarcomatoid features were more than > 10% of the tumor. The most common grade 3 or higher treatment-related adverse events included [11]:

- neutropenia (n = 20)
- anemia (n = 10)
- fatigue (n = 7).

CONCLUSION

The doxorubicin- and gemcitabine-based chemotherapy seems to be a favourable therapeutic option for patients in sarcomatoid component of the renal-cell cancer in which the nephrectomy was followed by the progression of the disease.

Based on literature data and own experience it seems that at present the optimum method of management of patients with renal cell carcinoma with sarcomatoid component is in the first line: surgery (including treatment of metastatic lesions) [1, 7] and in case of a failure, introduction of systemic treatment – doxorubicin and gemcitabine-based chemotherapy [2, 3]. It is important to examine **morphological feature of metastases which develop during the disease. Their character could be different than in the primary tumor. This may determine further action.**

The development of optimum method of systemic treatment requires further prospective randomised trials.

Acknowledgments

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Authors' contributions:
Agnieszka Gębara-Puchniarz: 40%, Rafał Stec: 20%, Beata Hryciuk: 10%
Cezary Szczylik: 10%, Wojciech Kozłowski: 10%, Bartłomiej Grala: 10%.