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Dramatic Response to Catumaxomab Treatment for Malign Ascites Related to Renal Cell Carcinoma With Sarcomotoid Differentiation

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Refractory malignant ascites (MA) is a common complication in cancer patients. Renal cell carcinoma (RCC) is rarely present with peritoneal ascites, which is commonly associated with carcinomas of the gastrointestinal and female reproductive tracts; including especially ovarian high-grade serous carcinoma. Currently, chemotherapy and paracentesis represent the most widely used methods to relieve the symptoms. Recently, intraperitoneal therapy with catumaxomab—a trifunctional hybrid antibody—has been introduced for the treatment of MA. The benefit of this treatment has been demonstrated in patients with distinct abdominal malignancies. In this case report, we present the first case of successful catumaxomab treatment against MA in a patient with advanced RCC with sarcomatoid differentiation. After the second administration of catumaxomab, paracentesis became no longer necessary. Catumaxomab might represent a safe treatment option for MA in the course of metastatic RCC with sarcomatoid differentiation.

Keywords: catumaxomab, malign ascites, renal cell carcinoma, sarcomatoid differentiation

INTRODUCTION

Refractory malignant ascites (MA) represents a common debilitating complication in patients with end-stage abdominal malignancies.[1] Renal cell carcinoma (RCC) rarely present with peritoneal carcinomatosis, which is commonly associated with carcinomas of the gastrointestinal and female reproductive tracts, including especially ovarian high-grade serous carcinoma.[2–6] It is caused by the invasion of the epithelial tumour cells into the peritoneal cavity. In spite of the symptomatic treatment options including repeated large-volume paracentesis, systemic chemotherapy, diuretics, and dietary salt restriction, efficient therapies are still lacking.[1,7] Finally, catumaxomab has been introduced as a novel therapy for MA. The trifunctional antibody (trAb) catumaxomab (Removab; Fresenius Biotech GmbH, Munich, Germany) is characterized by a unique ability to bind 3 different cell types: tumor cells, T cells, and accessory cells.[8–10] It was approved in the European Union (EU) in April 2009 for the intraperitoneal (i.p.) treatment of MA in patients with epithelial cell adhesion molecule (Ep-CAM)-positive carcinomas where standard therapy is not available or no longer feasible. Catumaxomab is the first trAb and the first drug in the world approved specifically for the treatment of MA.[11] It is the first substance worldwide with a regulatory label for the treatment of MA due to epithelial carcinomas. Because

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the peritoneum is of mesothelial origin and therefore lacks EpCAM expression, the i.p. administration of catumaxomab is an attractive targeted immunotherapeutic approach.[12] To date, positive results of catumaxomab treatment have been reported in cohorts of patients with advanced ovarian,[13] gastric, breast, pancreas, and endometrial tumors.[14,15] In the present report, we present the first case of successful treatment of MA in a patient with advanced RCC with sarcomatiod differentiation.

CASE REPORT

A 59-year-old patient with RCC with sarcomatiod differentiation had intermittent generalized abdominal pain for 6 months, which had increased in severity for 2 months before admission. A computed tomography (CT) scan of the thorax and abdominopelvic area was performed on July 16th, 2012. The scan showed a large mass in the right kidney, multiple metastases in both lungs and the liver, bilateral pleural effussion, peritoneal ascites, and peritoneal carcinomatosis. The biopsy performed on the right kidney in February 2012 revealed RCC with sarcomatoid differentiation. Interferon alpha therapy was started in May 2012. Because the PET-CT performed in September 2012 pointed to a progression with liver metastases and peritoneal ascites, the treatment regimen was changed to sunitinib 50 mg/d. The CT performed in November 2012 revealed peritoneal ascites and peritoneal implants (Figure 1). The first dose of the catumaxomab treatment was administered in December 14, 2012 and the second dose was given in December 17, 2012. The treatment was well tolerated and the only complication observed was grade 1 fever, which was premedicated with paracetamol before the treatment. The peritoneal ascites subsided after the second dose. The patient's treatment was continued with everolimus. The PET-CT was performed in March 6, 2013 and indicated pulmonary nodules, liver metastases, peritoneal implants, and regression in the mass located in the right kidney (Figure 2). A radical right nephrectomy was performed in March 26, 2013, and the analysis of the right renal mass revealed a RCC with sarcomatoid differentiation. The tumor measured 10 × 9 × 9 cm (approximately 60% of the tumor consisted of live tumor tissue, whereas 10–15% was necrotic tissue). There was an extensive lymphovascular invasion and the nuclear grade (Fuhrman) was 4. No invasion was observed in the renal capsule or the perinephritic adipose tissue. The immunohistochemical studies indicated diffuse and strong pancytokeratin positivity in the renal tumor. No HMB45 (human melanoma black-45) expression was observed in the renal tumor.

Between January and March 2013, the patient was treated with 5 mg/d of evorolimus. The imaging performed in September 2013 indicated no peritoneal ascites and the hepatic and pulmonary metastases were stable. The patient's treatment was continued with 10 mg/d of evorolimus.

DISCUSSION

RCC is the most common renal malignancy arising from renal tubular epithelium and constitutes 90% of renal malignancies in adults. Based on histology, RCC is classified into clear cell, papillary, chromophobe, and collecting duct carcinomas. The uncommon histological variants include medullary, mucinous tubular and spindle cell, tubulocystic carcinoma, and thyroid-like follicular carcinoma.[16–18]

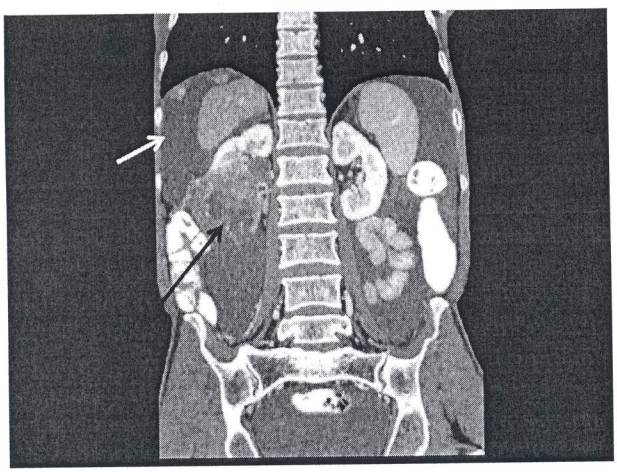

FIGURE 1. Liver and kidney masses before catumaxomab administration.

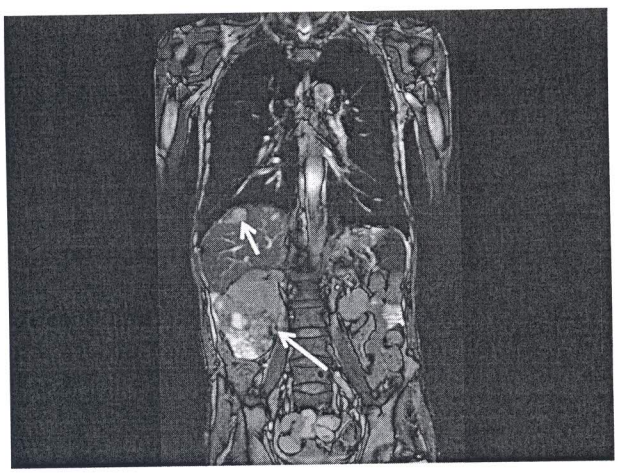

FIGURE 2. Liver and kidney masses after catumaxomab administration.

RCC with sarcomatoid differentiation (sarcomatoid RCC) is recognized as a distinct histological entity by the WHO classification of renal tumors (WHO, 2004) and is defined by the presence of foci of malignant spindle cells in any epithelial histological type of RCC. RCC with extensive sarcomatoid differentiation without any identifiable epithelial component is designated as unclassified RCC with sarcomatoid differentiation.[16,17] Sarcomatoid differentiation is observed in approximately 5% of all RCCs. However, a higher percentage (>50%) of sarcomatoid component is associated with poor prognosis. Approximately half of these patients present with distant metastases, and more than 80% of the patients die of disease. The median survival is <2 years.[19,20]

MA is an increased accumulation of protein-containing fluid within the peritoneal cavity, which is caused by i.p. spread of cancer. It is associated with advanced ovarian cancer, gastrointestinal malignancies, and other carcinomas and leads to abdominal pain and swelling, dyspnea, nausea, vomiting, fatigue, malnutrition, and anorexia.[21,22] Patients with MA have a poor quality of life.[21,23] The prognosis is poor with a median overall survival of approximately 1–6 months.[21,24,25]

The treatment of refractory ascites in patients with advanced abdominal malignancies is challenging.[26] Although repeated paracentesis—the most commonly performed procedure in patients with refractory MA—is regarded as a safe approach, hypotension, embolism, and secondary peritonitis have been reported as possible complications.[22] Recently, catumaxomab has emerged as a novel treatment modality for patients with MA.[13–15] Catumaxomab, a trAb, was reported to antagonize these mechanisms at the peritoneal tumor site by binding to EpCAM-positive tumor cells, T cells, and accessory cells.[27,28] The treatment consists of 1 cycle including 4 applications of i.p. catumaxomab at doses of 10, 20, 50, and 150 μg, on days 0, 3, 7, and 10, respectively. As a growing number of clinicians are using this new therapeutic option, the question has been raised if a second treatment cycle might be feasible and effective for patients who are benefited from the first cycle but eventually presented with recurrent ascites.[27]

During catumaxomab therapy, severe adverse effects might occur. The most common drug-related adverse events were cytokine release–related symptoms.[28,29] Burges et al[13] reported that fatigue, fever, and pain develop in 96% of the patients. In the same cohort, 70% of all patients suffered from gastrointestinal and hematological side effects (leukocytosis or lymphocytopenia in 30% of the patients).[13] These symptoms are because of the catumaxomab's mechanism of action and are well-known side effects of antibody therapy.[28,29]

Our patient was diagnosed with metastatic RCC and started systemic treatment as the MA occurred. After the second administration of catumaxomab, the patient's ascites was observed to have completely regressed. The patient did not need any paracentesis subsequent to the treatment. The imaging revealed close to full regression in the hepatic and pulmonary metastases and pleural effusion. Although this effect cannot be associated solely with catumaxomab because of the concomitant treatment with everolimus.

A possible explanation for the partial regression of liver metastases could be the minimal systemic absorption of catumaxomab into the general circulation. Ruf et al[30] reported the presence of systemic catumaxomab after the i.p. administration for treatment of MA in the vast majority of patients after the third and fourth infusion. However, the observed systemic catumaxomab exposure was low (<1%).[30] In a study performed on 14 patients with ovarian cancer, cytokeratin-positive cells were found in the peripheral blood in 57% of the patients before the catumaxomab therapy, whereas this ratio was only 42% after the therapy with catumaxomab.[14] However, a recently published case report demonstrated a systemic effect (regression of skin metastases) in a patient treated with catumaxomab for MA due to ovarian cancer, and this confirms the potential extraperitoneal benefit of the drug.[31]

In a patient with urothelial carcinoma accompanied by MA followed up by Krawczyk et al,[32] paracentesis was no longer needed after the treatment with catumaxomab.

Because the peritoneum is of mesothelial origin and therefore lacks EpCAM expression, the i.p. administration of catumaxomab is an attractive targeted immunotherapeutic approach.[12]

SUMMARY

Catumaxomab is an agent used in the treatment of MA, which contributes to paracentesis-free survival. Our patient is the first case where a full regression was observed after the second treatment with catumaxomab against MA associated with metastatic RCC with sarcomotoid differentiation.

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