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Intraperitoneal Catumaxomab for the Treatment of Malignant Ascites: 4 Cases

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ABSTRACT:

Intraperitoneal catumaxomab for the treatment of malignant ascites: 4 cases

Objective: To evaluate the efficacy of catumaxomab treatment for malignant ascites.

Cases: Four patients with malignant ascites who required paracentesis once or more a week and were considered for catumaxomab treatment, received catumaxomab following the therapeutical paracentesis, via intraperitoneal port catheter on the day 0., 3., 7. and 10. The frequency of paracentesis need and before and after the treatment wee compared and it was found that this frequency was decreased in each of the patients.

Conclusion: Catumaxomab therapy can be a good choice of treatment for the patients who suffer from malignant ascites and must be considered to improve particularly these patients' quality of lives.

Keywords: Catumaxomab, malignant ascites, palliative care

ÖZET:

Malign asit tedavisinde intraperitoneal catumaxomab kullanımı: 4 olgu

Amaç: Malign asit tedavisinde catumaksomab tedavisinin etkinliğinin gösterilmesi

Olgular: Malign asit nedeniyle haftada 1 ve daha sık parasentez ihtiyacı olup catumaksomab tedavisi planlanan mide kanserli 4 olguda terapötik parasentezi takiben intraperitoneal port kateteri yoluyla 0., 3., 7. ve 10. günlerde catumaksomab uygulandı. Tedavi sonrası ve öncesi parasentez ihtiyaçları karşılaştırılan hastaların herbirinde bu sıklığın azaldığı görüldü.

Sonuç: Malign asiti olan hastaların tedavisinde catumaksomab iyi bir seçenek olabilmektedir ve özellikle bu hastaların yaşam kalitelerinin arttırılması için göz önünde bulundurulması gerekmektedir.

Anahtar kelimeler: Catumaksomab, malign asit, palyatif kemoterapi

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INTRODUCTION

Malignant acid is caused by the obstruction of the lymphatic vessels resulting from malignant cell infiltration and the increased peritoneal permeability (1). Peritoneal carcinomatosis is present in two thirds of these patients. The most common malignant acid-related abdominopelvic cancers are the ovarian, pancreas, colon and endometrial cancers (2). Adenocarcinoma originating from abdominal organs is present in 75% of patients. The most common extra-abdominal malignancies are lymphoma, lung and breast cancers. Malignant acid is a poor prognostic marker for advanced stage cancer. Malignant acid should be considered when the serum-ascites albumin gradient (SAAG) is below 1.1gr/dL or ascitic fluid total protein level is above 2.5gr/dL (3). In particular, if the acid is haemorrhagic and the cell count is above 1000/mm^3, cytology is diagnostic in 50% of patients (4,5). Treatment is planned to reduce the severity of symptoms and providing general relief and improve the quality of life of the patient. Although large volumes of paracentesis are beneficial, palliation is transient. However, paracentesis can lead to some complications such as pain, hypotension,

perforation, peritonitis (6). Therefore, permanent treatment solutions for malignant ascites are still under investigation and new treatment methods are being tested. Catumaxomab is a chimeric antibody that has the potential to bind to the epithelial cell adhesion molecule (EpCAM) secreted by tumor cells, CD3 in T lymphocytes, and Fc gamma receptors (FcγR) on the surface of helper cells, and its use is becoming more and more common day by day (7,8).

MATERIAL AND METHOD

Patients with malignant ascites who required paracentesis once or more a week received catumaxomab treatment via intraperitoneal port catheter; 10 mcg on the day 0, 20 mcg on the day 3, 50 mcg on the day 7 and 150 mcg on the day 10.

CASE - 1

A 48-year-old male patient with peritoneal and omental implants had a pathology of gastric signet-ring cell carcinoma (SRCC) and the patient was considered inoperable. Docetaxel + Cisplatin + 5-Fluorouracil (5-FU) (DCF) was started as palliative chemotherapy. FOLFIRI (5-Fluorouracil (5-FU), folinic acid (FA), irinotecan) was initiated in the patient with detected progression at the 5th cycle of DCF protocol. Since the patient's need for paracentesis increased from once a week to 3 per week, catumaxomab administration was planned and intraperitoneal catumaxomab was administered after the second cycle of FOLFIRI treatment. Chemotherapy was replaced by the regimen EOX (epirubicin + oxaliplatin + capecitabine) as progression was observed under FOLFIRI regimen after 6th cycle. Patient requiring paracentesis only 3 times over 6 months after catumaxomab treatment is still under observation.

CASE - 2

A 37-year-old female patient who was diagnosed as gastric signet-ring cell adenocarcinoma (SRCC) with peritoneal and omental implants was considered inoperable and was referred to our outpatient clinic. Patient who received DCF as chemotherapy at the beginning started to undergo catumaksomab infusion on the basis of progression and malignant ascites detection. The treatment was continued with 3 cycles FOLFIRI regimen after progression was observed after catumaxomab. The patient was lost 4 months after the progression was detected. In this 4-month period, when paracentesis requirement frequency was compared before and after catumaxomab, it was seen that it decreased from 3 per weeks to once every 2 weeks.

CASE - 3

A 48-year-old male patient was diagnosed with gastric adenocarcinoma and after subtotal gastrectomy, liver metastases were detected and was referred to be evaluated for adjuvant chemotherapy. FOLFIRI regimen was initiated in the patient with progression after 5 cycles of cisplatin and capecitabine. The patient developed peritoneal carcinomatosis in the follow up, malignant ascites was detected and therapeutic paracentesis was needed once a week due to complaints of shortness of breath. Intraperitoneal catumaxomab was administered to the patient whose quality of life had reduced due to the need for paracentesis. The patient who was lost at the 3rd month after catumaxomab treatment, had been hospitalized due to the need for paracentesis only 3 times within the 3-months of period in which he had received FOLFIRI twice.

CASE - 4

A 43-year-old patient with gastric adenocarcinoma diagnosis was referred to the FOLFIRI regimen due to progression after 6 cycles EOF regimen (epirubicin + oxaliplatin + 5-fluorouracil). Intraperitoneal catumaxomab was administered to the patient who developed paracentesis once a week because of malignant accites in the 3rd cycle of FOLFIRI treatment. The need for paracentesis has been shown to decrease significantly from once a week to once a month and the patient is still being followed up under FOLFIRI treatment.

Table- 1: Data of 4 patients who received intraperitoneal catumaxomab for malignant acsictes treatment

Patient	**1**	**2**	**3**	**4**
Gender	Male	Female	Male	Female
Age	48	37	48	43
Date of Diagnosis	03.2013	09.2013	12.2012	07.2013
Origin of the Tumor	Stomach	Stomach	Stomach	Stomach
Pathological Diagnosis	Signet-ring cell adenocarcinoma	Signet-ring cell adenocarcinoma	Adenocarsinoma	Adenocarsinoma
Genetic Analysis	CerbB2 -	X	CerbB2 +3 FISH -	X
Metastasis	Peritoneum - omentum	Peritoneum - omentum	Liver	Multiple
Operation status	-	-	+	-
Chemotherapy	DCF FOLFIRI	DCF	Cisplatin capecitabine/ FOLFIRI	EOF FOLFIRI
Cycles	5+2	3	5+2	6+3
Pre-treatment paracentesis frequency	3/week	3/week	1/week	1/week
Date of Catumaxomab treatment	11.2013	12.2013	01.2014	01.2014
Side effects	Not observed	Not observed	Not observed	Not observed
Post-treatment paracentesis frequency	1 in 6 weeks	1 in 2 weeks	1 in 3 weeks	1 in 4 weeks
Post-Catumaxomab Chemotherapy	FOLFIRI+EOX	FOLFIRI	FOLFIRI	FOLFIRI
Number of post-Catumaksomab chemotherapyies	4+4	3	2	2
Mortality	Absent	6 months	15 months	Absent

CONCLUSION

Malignant ascites accounts for 10% of all causes of ascites (2). There are a number of factors that play a role in ascites pathophysiology. There are five types of barrier systems that prevent proteins to be trasnported from peritoneum. These include capillary endothelium, capillary basement membrane, insterstial stroma, mesothelial basal membrane, and mesothelial cells in the peritoneal membrane. Proteins collected in the peritoneal cavity return to the intravascular area by the peritoneal lymphatic system (9). Vascular permeability, which is responsible for the peritoneal fluid balance, and damage to the lymphatic drainage are the main causes of malignant ascites formation. Cytologic examination supports the diagnosis of malignant ascites if the serum-ascites albumin gradient (SAAG) is below 1.1gr/dL and the total protein level is above 2.5gr/dL (3). Where these are present, treatment should focus on relieving symptoms, rather than prolonging survival, such as nausea, vomiting, abdominal pain, dyspnea and loss of appetite due to ascites. When the patient is diagnosed with malignant ascites, the surveillance expected despite all treatments is shorter than 16 weeks.

In a 2009 review, among treatments that have been used or being used for malignant ascites; diuretics, paracentesis, peritovenous shunts, intraperitoneal chemotherapies, intraperitoneal TNF-α, interferon (IFN α-2b), anti-VEGF, immunomodulators (streptococcal antigen - OK-432), metalloproteinase inhibitors and catumaxomab were mentioned (10). It is stated that of these treatments, the efficacy of diuretic treatment is controversial and because peritoneovenous shunt

is performed under general anesthesia, it is a risky intervention which prevents its use in such patients (11). Data on anti-VEGF use are only yet available with animal experiments; interferon and immunomodulator treatments are also limited to phase 2 studies (12,13).

The side effects of intraperitoneal agents given to reduce the systemic effect of chemotherapeutic agents, such as intraabdominal infection, catheter infections, catheter leakage and obstruction, abdominal pain, adhesion, abcess, ileus, perforation and necrosis have been revealed. At the same time, in case of localized malignant ascites, the spreading of the molecules inside of the peritoneal cavity constitutes another problem. Mitoxantrone has also been tried intraperitoneally and can be better tolerated; however, there is not enough data in the relevant studies (14,15).

Today, intraperitoneal treatments such as catumaxomab, the first FDA-approved molecule for the treatment of malignant ascites in epithelial cancers, have begun to be successfully applied. Catumaxomab is a chimeric antibody that has the potential to bind to the epithelial cell adhesion molecule (EpCAM) secreted by tumor cells, CD3 in T lymphocytes, and Fc gamma receptors (FcγR) on the surface of helper cells (7,8). This binding results in the release of proinflammatory cytokines such as interferon-γ, tumor necrosis factor-α, IL-2 and IL-6, and the reduction of EpCAM positive cells through association with macrophages, dendritic cells and natural killer cells (16-18). Thus, catumaxomab is a new therapeutic modality that is promising, especially in terms of quality of life. We shared the results we achieved with these treatment modalities in our 4 cases. All our four patients had adenocarcinoma or Siglet-ring cell variant of adenocarcinoma and metastasis was present in different regions with peritoneum. During the follow-up of patients with chemotherapy, patients were admitted to the hospital with complaints such as dyspnea, nausea, vomiting and limitation of movement due to malignant ascites. Despite adequate supportive care, the high rates of paracentesis requirements restricted the quality of life of these patients with a very negative effect. Based on the information available in the literature since 2009, we administered intraperitoneal catumaxomab therapy to our patients with maximal supportive treatment. None of the patients had a side effect related to catumaxomab. Chemotherapy regimens were continued following catumaxomab administration after 3 weeks. The mean paracentesis requirement for all patients before the administration was 2 (1 to 3) per week whereas this rate was observed to be less than 2 (1 to 2) per month after catumaxomab administration (Table-1). Two of our patients were lost about 3 months after catumaxomab treatment, while the other two patients are still being followed. With the need for paracentesis, there was a decrease in symptoms such as nausea, vomiting, dyspnea, limitation of movement and abdominal pain, and relatviely, a significant increase in the quality of life of the patients was observed.

In conclusion, the use of biologic therapies in combination with palliative treatment in terminal cases with malignant ascites in this case series plays an important role in eliminating the symptoms of the patients and, consequently, in raising the quality of life and should be considered in the treatment planning. In terms of survival, although there is no direct effect of catumaxomab, there is an increase in the chance of receiving chemotherapy with the increase in quality of life, which may indirectly have a positive effect on patients' survival.

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