Intraperitoneal Nivolumab for Malignant Ascites in Patients with Advanced Gastrointestinal or Pancreaticobiliary Tract Cancer

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Introduction

Malignant ascites occur in 10 – 15% of patients with cancers from gastrointestinal tract, and it leads to impaired quality of life and declined performance. The ineffectiveness of systemic chemotherapy in the treatment of malignant ascites is largely due to inefficient intravenous delivery of anticancer drugs to peritoneal carcinomatosis. The unfavorable therapeutic gradient for anticancer drug delivery is related to the high interstitial fluid pressure caused by the dense extracellular matrix around cancer cells and chaotic networks of neo-vessels from tumor angiogenesis. Otherwise, the abundance of immune cells in the peritoneum and ascites, as well as the immune escaped circumstance created by cancer cells in the peritoneum, suggest the potential use of intraperitoneal (IP) immune checkpoint inhibitors to control malignant ascites.

Materials and Methods

Patients with cancers from gastrointestinal or pancreaticobiliary tract who had cytologically confirmed malignant ascites were enrolled. 20mg of nivolumab diluted in 100ml of saline was infused into the peritoneal cavity in 10 minutes after paracentesis. IP therapy was repeated after each paracentesis until ineffectiveness of therapy judged by physician, unacceptable toxicity, or patient's refusal. The clinical response and adverse effects were recorded. The cellular components of malignant ascites sampled prior each paracentesis were analyzed by flowcytometry.

Results

Totally, 9 patients with a median age of 55 years were treated with IP nivolumab. The cancer types were pancreatic cancer in 4, biliary tract cancer in 3, and gastric cancer in 2 patients. Systemic anticancer treatments were given for 3 lines in 2, 2 lines in 2, and 1 line in 4 patients before the administration of IP nivolumab. All of them did not receive any local treatment for the malignant ascites before. All patients had a second course of IP nivolumab between the fifth and seventh days after the first course. Subsequently, IP nivolumab was administered after paracentesis according to the symptoms of abdominal fullness. The median treated cycles and period of ascites control were 3 and 33 days, respectively.

7/9(77%) patients had clinical response as evidenced by reduced ascites and less frequent paracentesis. The change of tumor cell number in serial ascites, instead of the change of lymphocyte counts and lymphocyte percentage, correlated with the clinical response. There was only grade 1 tenderness over the puncture site as the adverse effect. The reasons of stop IP were death due to disease progression in 5, patient's wish in 2, and clinical unresponsiveness in 2 patients, respectively.

Table 1. Characteristics of patients and ascites content. Responder / Non-Responder

Patient	Age	Sex	Cancer	Prior systemic anticancer therapies	Total cycles of IP	Cancer cells in ascites (/cumm)		Clinical response	Duration of response (days)	Cause of stop IP
						Before IP Nivo	After IP Nivo			
a	55	M	PC	2	2	.258	.252	Y	28	PW
b	53	F	PC	0	4	.517	.364	Y	48	D
c	52	F	PC	2	5	1.063	.117	Y	64	D
d	71	M	BTC	1	3	1.586	.552	Y	38	PW
e	53	F	PC	1	2	1.976	1.007	Y	29	D
f	71	F	BTC	3	3	3.277	.089	Y	40	D
g	55	M	GC	3	5	24.381	9.163	Y	37	D
i	69	M	BTC	1	2	7.254	11.788	N	10	NR
h	48	F	GC	1	2	4.016	7.115	N	28	NR

Abbreviation: BTC, biliary tract cancer; D death; F, female; GC, gastric cancer; IP, intraperitoneal; M, male; N, no; Nivo, Nivolumab; NR, no response; PC, pancreatic cancer; PW, patient wish; Y, yes

Figure 1. The change of tumor cell number in ascites before and after intraperitoneal administration of nivolumab. Each line represented for one individual. The tumor cells were analyzed using ascites taken in paracentesis before administration of intraperitoneal nivolumab.

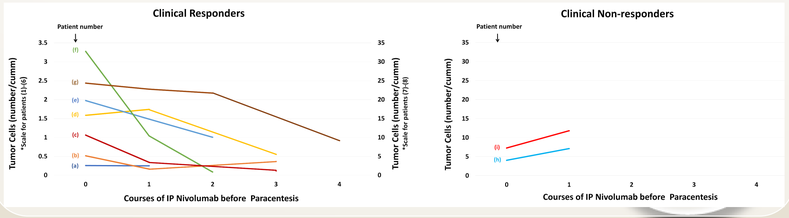


Figure 2. The change of lymphocyte count in ascites before and after intraperitoneal administration of nivolumab. Each line represented for one individual. The lymphocytes were analyzed using ascites taken in paracentesis before administration of intraperitoneal nivolumab.

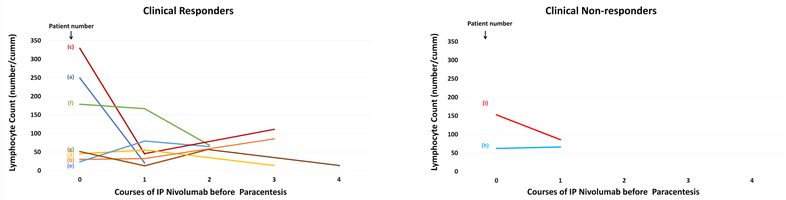
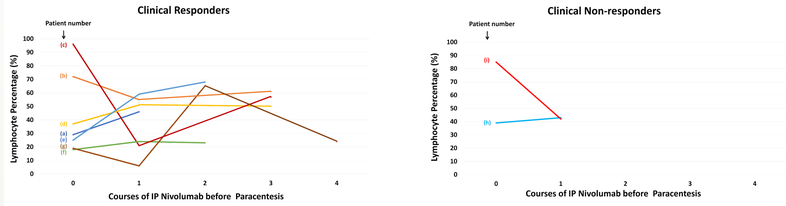


Figure 3. The change of lymphocyte percentage in ascites before and after intraperitoneal administration of nivolumab. Each line represented for one individual. The lymphocytes were analyzed using ascites taken in paracentesis before administration of intraperitoneal nivolumab.



Conclusions

- IP administration of nivolumab was a safe and effective method to control malignant ascites from gastrointestinal or pancreaticobiliary tract cancer.
- The clinical effect is also related to the change of tumor cells in malignant ascites.
- Further validation of the application in larger population and other types of cancer, as well as biomarkers study are needed.

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The authors declare no conflicts of interest

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