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Research Article

Association of Serum Interleukin-6 and Interleukin-8 Levels with Clinical Benefit from Immune Checkpoint Inhibitors in Patients with Advanced Gastric Cancer

Liang Han,* **Yuan Yuan,*** **Yu Feng,** **Xiaowu Li**

Department of Medical Oncology, Xuzhou Central Hospital, Xuzhou, China
These authors contributed equally to this work.

Abstract

Objectives: This study mainly analyzes the association between serum interleukin-6(IL-6) and interleukin-8(IL-8) levels and clinical benefit from immune checkpoint inhibitors in patients with advanced gastric cancer.

Methods: The clinical characteristics of 51 patients with advanced gastric cancer, diagnosed in our hospital and treated with immune checkpoint inhibitors, were analyzed retrospectively in our study.

Results: After three cycles of immunotherapy, the level of serum IL-6 decreased in 10 patients (37%) and the level of serum IL-8 decreased in 27 patients (52%). Compared with patients with increased serum IL-6 level, patients with decreased serum IL-6 level tended to have higher partial response (PR), stable disease (SD), but the difference was not statistically significant. Compared with patients with increased serum IL-8 level, there were significant differences in PR, SD for patients with decreased serum IL-8 level($P \leq 0.05$). Patients with decreased serum IL-6 or IL-8 levels tended to have better progression-free survival(PFS) and overall survival(OS) than those with increased serum IL-6 or IL-8 levels.

Conclusion: The changes in IL-6 and IL-8 levels could be as predictive indicators to predict benefit from immune checkpoint inhibition in advanced gastric cancer. Patients with decreased serum IL-6 or IL-8 levels during immunotherapy may achieve better clinical benefit.

Keywords: Gastric cancer, interleukin-6, interleukin-8, immune checkpoint inhibitor

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In recent years, with the clinical research of immune checkpoint inhibitors made a breakthrough,[1-2] immunotherapy has become an important treatment for advanced gastric cancer. However, the efficacy of monotherapy for immune checkpoint inhibitors is generally low (ORR about 15%), and most patients are still not confirmed to benefit from immune checkpoint inhibitors.[3] Therefore, the exploration of efficacy prediction indicators is particularly important, It can not only screen the effective population, but also avoid unnecessary economic losses and drug related risks. The expression of programmed cell death receptor ligand 1 (PD-L1), microsatellite instability (MSI) and Epstein Barr virus (EBV) has been reported to be able to effectively evaluate the efficacy of immunotherapy in advanced gastric cancer,[4-6] but the indicators above are not routine tests and are expensive. At present, several studies[7-9] have showed that the serum IL-6 and IL-8 levels before and during immunotherapy is closely related to the immune status of body and the efficacy of immunotherapy in several advanced cancers. However, the information concerning patients with advanced gastric cancer is limited. Thus a retrospective analysis of patients with advanced gastric cancer

Address for correspondence: Xiaowu Li, MD. Department of Medical Oncology, Xuzhou Central Hospital, Xuzhou, China
Phone: +90-0516-83956345 **E-mail:** Lixw958@163.com

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was conducted by investigating the association between changes in serum interleukin-6 and interleukin-8 levels and clinical benefit from immune checkpoint inhibitors in patients with advanced gastric cancer.

Methods

Patients

We carried out a retrospective study of 51 patients with advanced gastric cancer who received immune checkpoint inhibitors as first, second or more line treatment. All of them were diagnosed at a single institution. The diagnostic criteria was based on histopathological criteria (the World Health Organization, 2004). Clinical information was obtained from archived medical records. This study was approved by the institutional subcommittee and ethics committee. informed patient consent were obtained.

The immune checkpoint inhibitors in our study mainly includes sintilimab, tislelizumab, camrelizumab. The modes of immune checkpoint inhibitors include single drug, combined chemotherapy, antiangiogenic agents.

Observation Index

Serum levels of interleukin-6 and interleukin-8 were obtained using enzyme linked immunosorbent assay (ELISA) before and after three cycles of immunotherapy. The criteria for determining increase of serum IL-6 and IL-8 levels were IL-6≥5.9pg/mL and IL-8≥20.6pg/mL, respectively.

The best response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST v1.1). Objective tumor responses included complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The disease control rate (DCR) was defined as the addition of objective response and stabilization rates (CR + PR + SD).

Primary endpoints of our survival analysis were overall survival (OS) and progression-free survival (PFS). OS was measured from the date of diagnosis until the date of death due to any cause, or the date of survivors' final follow-up. PFS was calculated from the date of diagnosis to the date of treatment failure, relapse, evidence of disease progression, or death due to any cause.

Statistical Analysis

The continuous variables of serum cytokines were compared by t-test. The counting data were compared by c2 test. Survival curves were estimated by the Kaplan-Meier method. Survival curves were compared using the log-rank test. The SPSS 17.0 software (SPSS, Inc., Chicago, IL, USA) was used for statistical analyses.

Results

Patient characteristics are shown in Table 1. Of 51 patients with advanced gastric cancer, 29 were male and 22 were female [male/female (M/F) ratio, 1.3:1], with a median age of 56 .5years (range, 32-88 years). The most common complaints were abdominal pain or discomfort, weight loss, poor appetite, nausea and vomiting. Macroscopically, the most commonly involved site was the antrum (20/51, 39%), followed by the corpus (13/51, 25%), and fundus (18/51, 36%). All patients received immune checkpoint inhibitors as first-line (14/51, 27%) or second or more line (37/51, 73%) treatment. Before treatment, the average IL-6 level for all patients was 11.4pg/ml (0.6 ~ 78.2 pg/ml), the average IL-8 level was 37.8pg/ml (2.3 ~ 167.3pg/mL). After three cycles of immunotherapy, the average level of IL-6 was decreased in 10 patients with average level 9.2 pg/ml (1.3 ~ 45.9 pg/mL) the average level of IL-8 was decreased in 27 patients with average level 19.7pg/ml (10.3 ~ 71.9 pg/mL).

Short term Efficacy

Before the deadline of follow-up, the best response was available for all patients.The ORR and DCR were 23% (12/51) and 66% (34/51) respectively. CR was achieved in

Table 1. Characteristics of 51 patients with advanced gastric cancer

Characteristics	No (%)
Sex	
Male	32 (62)
Female	19 (38)
Median age (range)	60 (56-80)
ECOG performance status	
0-1	35 (68)
≥2	16 (32)
Staging	
III	2 (4)
IV	49 (96)
Histologic grade	
G1	0 (0)
G2	10 (19)
G3	29 (56)
Gx	12 (25)
Previous therapies	
First-line	14 (27)
Second or more line	37 (73)
IL-6	
Decreased	10 (19)
Increased	41 (81)
IL-8	
Decreased	27 (52)
Increased	24 (48)

0% (0/51), PR in 23% (12/51), SD in 43% (22/51), and PD in 34% (17/51). After three cycles of immunotherapy, the average IL-6/IL-8 levels in group 1 of disease control were significantly reduced, compared with group 2 of disease progression ($p \leq 0.05$) (Table 2). Compared with patients with increased IL-6, patients with decreased IL-6 tended to have higher percentage of PR, SD, but the difference was not statistically significant. Compared with patients with increased IL-8, the differences in percentage of PR, SD for patients with decreased IL-8 were statistically significant ($p \leq 0.05$) (Table 3).

Survival Analysis

The median time of follow-up was 6.4 months (range, 1.6-14.1months). The median PFS of the entire population was 3.8 months (range, 1.6-14.1 months), and the median OS was 9.7 months (range, 2.4-13.2 months) (Fig. 1). During immunotherapy, compared with patients in group 2, patients in group 1 tend to have better prognosis. There were statistically significant difference in PFS and OS between two groups, the median PFS of patients in group 1and group 2 were 5.0 months and 3.1 months, the median OS were 15.0 months and 9.0 months (Fig. 2).

Discussion

According to the latest cancer report released by the National Cancer Center,[10] gastric cancer is the third most commonly diagnosed cancer and is also the third leading cause of cancer-related deaths in china, with approximately 480000 new cases (10.5%) and 370000 deaths. Due to lack of typical symptoms in early stage of gastric cancer patients, once diagnosed, more than 70% of the patients have been in advanced stage, and have lost the opportunity of surgery. Combination regimens,[11,12] including a fluoropyrimidine and a platinum agent (plus an anti-HER2 monoclonal antibody for HER2- positive cases) at first-line and paclitaxel with or without ramucirumab at second-line are traditional treatment methods for advanced gastric cancer, with disappointing ORR of 34.8% and OS of 11.6 months. In recent years, with the clinical research of immune checkpoint inhibitors made a breakthrough, immunotherapy has become an important treatment for advanced gastric cancer. The immune checkpoint inhibitors mainly includes nivolumab, pembrolizumab, sintilimab, tislelizumab, etc. The modes of immune checkpoint inhibitors include single drug, combined chemotherapy or antiangiogenic agents.[13] The nivolumab is the first breakthrough, establishing a new immunotherapy standard for first-line treatment of advanced gastric cancer. In the CheckMate 649 trial,[14] nivolumab plus chemotherapy resulted in significant improvements in OS and PFS, versus chemotherapy alone. Besides, a subgroup analysis of Asian populations found nivolumab plus chemotherapy showed better clinical efficacy than the overall population. The median OS of patients with PD-L1 CPS ≥5 was 14.3 in the nivolumab plus chemotherapy group and 10.3 months in the chemotherapy group. Sintilimab is a domestically developed immune checkpoint inhibitor to be marketed in China. In the phase III ORIENT16 trial,[15] Sintilimab plus chemotherapy can also achieve excellent results in the treatment of advanced gas-

Table 2. Changes of average serum IL-6/IL-8 levels according to efficacy

Groups	No. of assessable patients (%)	Change in IL-6 (pg/ml)		Change in IL-8 (pg/ml)	
		Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Group 1 (PR+SD)	34 (67)	17.0	7.1	35.5	15.1
Group 2 (PD)	17 (33)	16.7	19.6	12.0	18.9
t	-	0.075	-7.406	1.244	-2.198
p	-	0.94	<0.01	0.219	0.033

Table 3. The best overall response category according to changes in serum IL-6/IL-8 levels

Outcome	No. of assessable patients (%)		p	No. of assessable patients (%)		p
	Decreased in IL-6	Increased in IL-6		Decreased in IL-8	Increased in IL-8	
CR	0	0	-	0	0	-
PR	8 (16)	4 (8)	0.21	10 (20)	2 (4)	0.03
SD	17 (33)	5 (10)	0.72	15 (29)	7 (14)	0.05
PD	16 (31)	1 (2)	0.13	2 (4)	15 (29)	<0.01

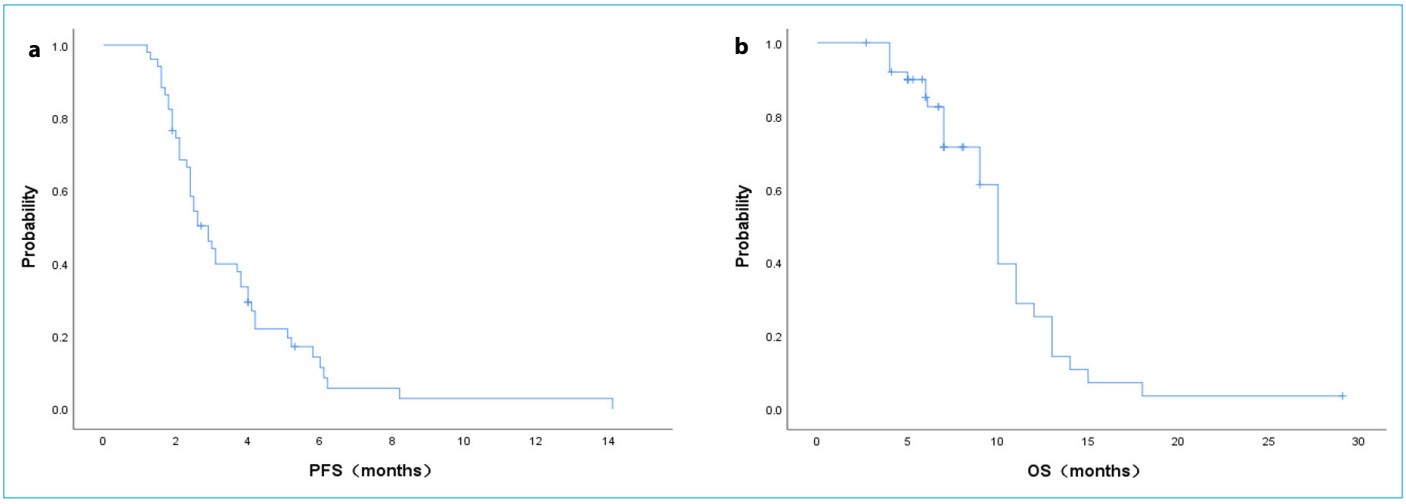

Figure 1. Survival curves for the entire population of 51 patients. **(a)** Progression-free Survival (PFS); **(b)** Overall Survival (OS)

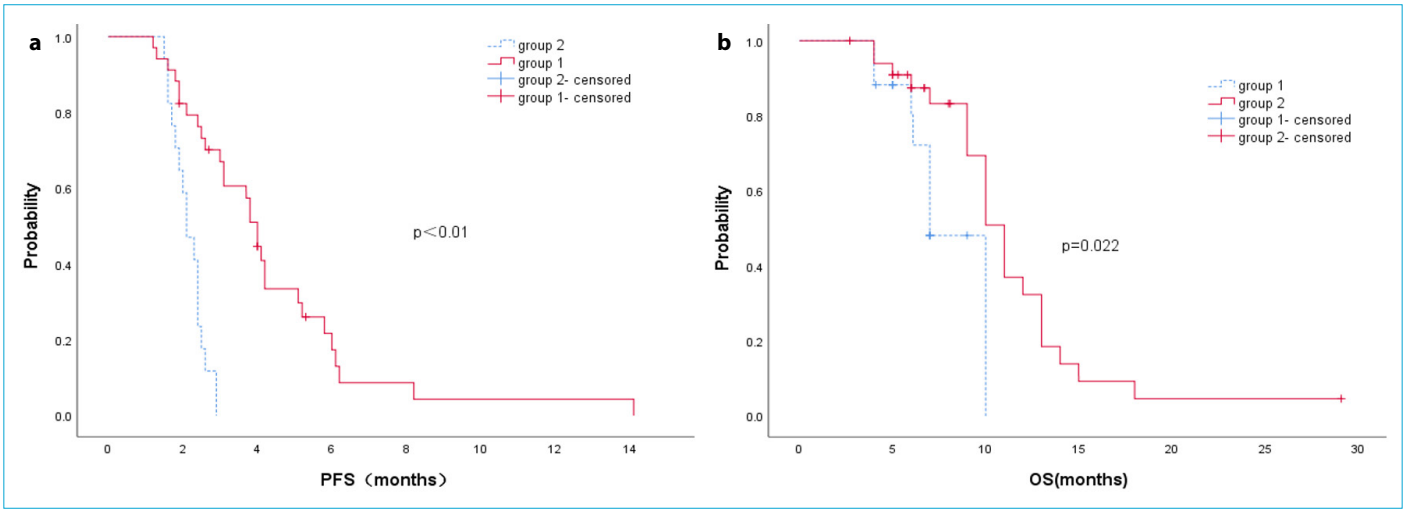

Figure 2. Comparison of the survival curves for patients in group 1and group 2. **(a)** Progression-free Survival (PFS); **(b)** Overall Survival (OS)

tric cancer, with a median OS improvement of 5.5months. According to the interim results of KEYNOTE-811,[16] pembrolizumab have received accelerated approval by the Food and Drug Administration (FDA) in combination with standard treatment for patients with HER2 positive advanced gastric cancer.

However, the effective rate of monotherapy of immune checkpoint inhibitor is generally low (ORR about 15%). As there is no reliable predictive indicators to predict benefit from immune checkpoint inhibition, most patients have not been confirmed to benefit from immunotherapy. Although several indicators (including PD-L1, MSI, EBV, etc) have been examined to identify susceptibility to immune checkpoint inhibitor, the indicators above are not routine tests, which require immunohistochemical or genetic testing.

Recent studies[8,9] demonstrate that changes in serum IL-6 and IL-8 levels are associated with improved outcomes with immunotherapy in advanced cancer. Theoretical basis was that both of them has immunosuppressive functions and may drive a myeloid compartment that contributes to innate treatment resistance. Keegan A et al.[8] measured plasma 12 cytokines in patients with advanced lung cancer before and during treatment with immunotherapy. They observed that decreases in serum IL-6 level are associated with improved outcomes with immunotherapy in advanced lung cancer. Kurt A et al.[5] reviewed 1344 patients to evaluated the effect of serum IL-8 levels on immunotherapy in patients with advanced cancer from four randomized phase 3 clinical trials(including melanoma, lung cancer,renal-cell cancer). A strong association was found between tumor IL-8 level and tolerogenic myeloid-cell infiltration in the tumor microenvironment. Nonetheless, the available data on advanced gastric cancer is limited.Thus, we conducted this retrospective analysis to evaluate the relationship between changes of IL-6 and IL-8 before and during immunotherapy and clinical benefit. In our study,

increased IL-6 and IL-8 occurred more frequently in patients with advanced gastric cancer, similar to recent studies. The median PFS of patients with decreased IL-6 and increased IL-6 were 5.0 and 3.1 months (p=0.089), the median OS were 15.0 and 9.0 months (p=0.006). The median PFS of patients with decreased IL-8 and increased IL-8 were 4.3 and 2.6 months (p=0.003), and the median OS were 11.6 and 8.6 months (p=0.056). Compared with patients in increase group, patients in decrease group of IL-6 or IL-8 tend to have better prognosis. Our results seem to further strengthen the current hypothesis that the changes in IL-6 and IL-8 levels could be as predictive indicators to predict benefit from immune checkpoint inhibition. However, as the number of patients in our study is extremely limited, larger scale, prospective, randomized clinical studies are needed in the future.

Disclosures

Ethics Committee Approval: This study was approved by Xuzhou Central Hospital Ethics Committee (Date: 4/7/2022, Number: XZEC-2022-047).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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