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ORIGINAL RESEARCH

Effect of Immune Checkpoint Inhibitors Plus Chemotherapy on Advanced Gastric Cancer Patients with Elevated Serum AFP or Hepatoid Adenocarcinoma

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Purpose: Alpha-fetoprotein-producing gastric cancer (AFPGC) and hepatoid adenocarcinoma of stomach (HAS) are rare types of gastric cancer, with specific clinical manifestations and poor prognosis. The standardized treatment process of such cancers remains elusive. We aim to investigate the efficacy of immunotherapy combined with chemotherapy on patients with AFPGC or HAS.

Patients and Methods: AFPGC and HAS patients who underwent immunotherapy and/or chemotherapy as the first-line treatment at our institute from June 2016 to December 2018 were enrolled in this observational study. Their clinicopathological characteristics, serum AFP level and treatment methods were collected. The progression-free survival (PFS) and overall survival (OS) were analyzed and compared between patients who received immunotherapy plus chemotherapy and those received chemotherapy.

Results: A total of 21 patients with advanced AFPGC or HAS were included in the study and the median follow-up time was 28.0 months. Of the 21 patients, 7 patients received immunotherapy of PD-1 antibody (nivolumab) plus chemotherapy and 14 patients as control received chemotherapy with or without Herceptin/Apatinib. The median progression-free survival (mPFS) time was 5.0 months (4.3 months in the control group and 22.0 months in the immunotherapy group). The median overall survival (mOS) time of the control group was 16.0 months (14.0 months in chemotherapy alone subgroup, 20.0 months in chemotherapy plus Apatinib or Herceptin subgroup), while the mOS of patients receiving immunotherapy was not reached.

Conclusion: This study suggested PD-1 checkpoint inhibitor plus chemotherapy could benefit AFPGC and HAS patients. Its mechanism of action warrants further investigation.

Keywords: gastric cancer, immunotherapy, alpha-fetoprotein-producing gastric cancer, hepatoid adenocarcinoma of stomach

Introduction

Gastric cancer (GC) is a highly heterogeneous tumor. Alpha-fetoprotein-producing gastric cancer (AFPGC) and hepatoid adenocarcinoma of the stomach (HAS) are special and rare subtypes of gastric cancer. AFPGC, first described as a case of gastric cancer with liver metastasis by Bourreille et al in 1970, is positive for AFP in serum and pathological specimen.[1] Since then, it has been reported all over the world but mostly in Asia, with an estimated incidence of 2.37.1% among all gastric

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cancers.[2] As a diagnostic basis, serum AFP levels of most AFPGC were only slightly higher than normal, but in some cases, the serum AFP levels were even beyond the detection limit.[3–5] In some AFPGCs, it was observed that certain lesions mimicked HCC-like morphology under a light microscope. The lesions were composed of large, polygonal cells with abundant eosinophilic cytoplasm. Ishikura et al proposed the term "hepatoid adenocarcinoma of the stomach" for a gastric cancer with the histological features of hepatocytic differentiation.[6] Therefore, AFPGC and HAS have overlapping but distinct populations. The former is more concerned with serum AFP level, while the latter is mainly focusing on pathological morphology. AFPGC and HAS patients have unique clinicopathological features, which are prone to liver and lymph node metastasis with a poor prognosis.[7–9] At present, there is no individualized treatment for these types of gastric cancer. Treatment approaches have mainly followed principles for the treatment of common gastric cancer.

Recently, immunotherapy has shown some effect in the treatment of advanced gastric cancer. ATTRACTION-2 and KEYNOTE-059 studies have proved the efficacy of PD-1 mAb in the third-line treatment of gastric cancer.[10,11] However, the effectiveness of PD-1 antibody in the first-line treatment of gastric cancer is still controversial. The Phase III RCT clinical study KEYNOTE-062 showed that PD-1 antibody combined with chemotherapy was not superior to chemotherapy in the first-line treatment of gastric cancer.[12] The results of the CheckMate 649 study reported in ESMO 2020 indicated that PD-1 antibody (nivolumab) had a survival advantage over chemotherapy alone (PFS 7.7 vs 6.9 months, OS 13.8 vs 11.6 months).[13] However, the improvement was still not ideal. To our knowledge, there are no published data on the effectiveness of immunotherapy for HAS/AFPGC.

To explore whether immunotherapy can improve the prognosis of these subtypes of gastric cancer, we conducted a real-world study.

Patients and Methods

Patients

Since June 1, 2016, advanced gastric cancer patients, who accepted first-line treatment in Zhongshan Hospital, Fudan University, were included in the registration queue according to their serum AFP and pathological characteristics. The last registration time and follow-up time were December 31, 2018 and March 1, 2020, respectively. This study was approved by the Ethics Committee of Zhongshan Hospital of Fudan University (B2020-094R) and conducted in accordance with the Declaration of Helsinki. Written informed consent had been obtained.

Inclusion criteria: 1) unresectable advanced or locally advanced gastric adenocarcinoma, 2) AFPGC was defined as an increase of serum AFP (more than 20 ng/mL) without accompanying chronic hepatitis, fatty liver, cirrhosis or other basic diseases. HAS was evaluated and diagnosed as primary gastric cancer exhibiting a typical hepatoid component by two pathologists based on the World Health Organization system.[14]

Methods

The clinical characteristics, treatment, efficacy, and adverse reactions of these patients were collected. The curative effect was evaluated according to RECIST 1.1 standard. The evaluation of adverse events was based on the Common Terminology Criteria for Adverse Events V4.0 (CTCAE). The primary endpoints were PFS and OS.

Serological AFP level was also collected. The cut-off value for serum AFP was 20 ng/mL, which is the upper limit of normal reference value of AFP in our hospital laboratory. The patients were divided into two groups, immunotherapy group and control group, based on the treatment regimen.

Pathological Specimen

Hematoxylin and eosin (HE) stained sections were retrieved from GC patients with elevated serum AFP or patients diagnosed as HAS and re-evaluated by another pathologist (Figure 1). Based on HE staining, the samples were classified by Lauren classification into intestinal, diffuse, or mixed type. The expression of PD-L1 (programmed cell death ligand 1) was detected by immunohistochemical assay (SP263) and evaluated using combined positive score (CPS). PD-L1 positive was defined as CPS $\geq$ 1. Tumor micro-satellite instability (MSI) status was evaluated by MLH1, MSH2, MSH6 and PMS2. EBV small RNA (EBER1) expression was detected by in situ hybridization method.

Statistical Analysis

SPSS 20.0 software and GraphPad Prism 5.0 were used for statistical analysis. The Chi-square Test was used for correlation tests. Kaplan-Meier method was performed for survival curve analysis. Log-rank was used for significance testing, and $P<0.05$ was considered statistically significant.

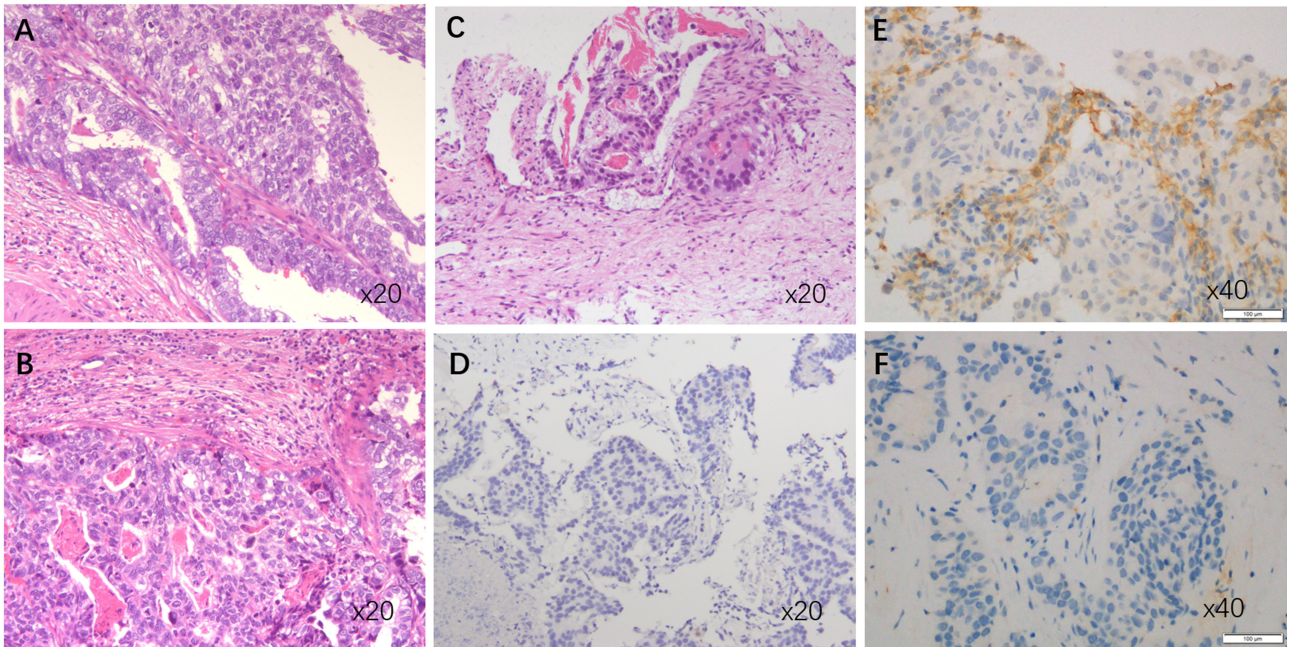

Figure 1 Histologic features of AFPGC and HAS. (**A**) HE staining of primary lesion of HAS. (**B**) HE staining of metastatic lesion of the same HAS patient as (**A**). (**C**) HE staining of AFPGC sample without typical HAS. (**D**) Immunohistochemical staining for AFP (negative) of AFPGC sample without typical HAS. (**E**) PD-L1 positive sample by immunohistochemical staining with SP263. (**F**) PD-L1 negative sample by immunohistochemical staining with SP263.

Results

From June 2016 to December 2018, 564 cases were diagnosed as advanced gastric cancer in our hospital. Twenty-one patients were enrolled in the study with 19 serum AFP positive patients, and 13 cases confirmed as HAS. In patients diagnosed as HAS, 11 patients were with high serum AFP level at the same time (Figure 2).

Among the 21 patients, there were 4 females and 17 males (Table 1). The median age of the patients was 65 years old. The most common pathological type was intestinal type (10 cases, 47.6%), followed by diffuse type (7 cases, 33.3%) and mixed type (4 cases, 19.0%). All 21 patients were micro-satellite stable (MSS). Nineteen patients were tested for EBER1 gene expression and all of them were negative. The primary location of tumor was stomach (15/21, 71.4%) and GEJ (6/21, 28.6%). There were 3 (14.3%) patients with HER-2 amplification and 17 (81.0%) patients with liver metastasis. Ten patients were PD-L1 positive (CPS ≥1).

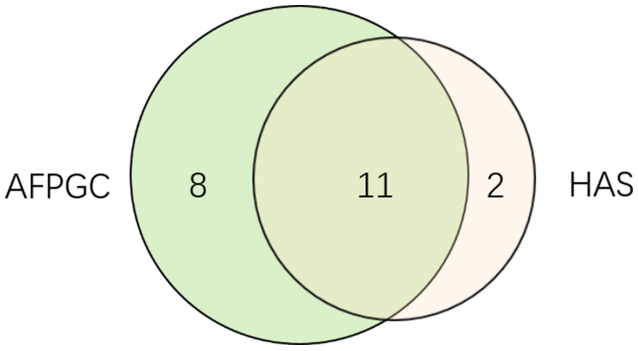

Figure 2 The distribution of AFPGC and HAS in enrolled patients. Nineteen patients were with AFP positive and 13 patients were diagnosed as HAS. Eleven HAS patients had high serum AFP.

Seven patients were treated with PD-1 antibody plus chemotherapy, and 14 cases received chemotherapy as the first-line treatment (six patients were administered with XELOX in 3-week treatment cycles) (intravenous oxaliplatin 130 mg/m^2 on day 1, oral capecitabine 1000 mg/m^2 twice daily from day 1 to 14). Two patients received DOS regimen: docetaxel 40 mg/m^2 and oxaliplatin 100 mg/m^2 on day 1 plus S-1 40 mg/m^2 orally twice daily from day 1 to 14 every 3 weeks. Three patients received oral apatinib 500mg qd combined with XELOX. Another three patients were HER-2 positive, receiving XELOX combined with Herceptin. In the immunotherapy group, all patients were treated with 360 mg of nivolumab combined with XELOX every 3 weeks.

In terms of efficacy, ORR was 85.7% in immunotherapy group and 21.4% in control group (P = 0.005, Table 2). The mPFS time was 5.0 months for the first-line treatment, with 4.3 months in the control group, and 22.0 months in the immunotherapy group (Figure 3A, P=0.01).

In the chemotherapy group, 12 patients received second-line treatment (6 chemotherapy, 3 immunotherapy, and 3

Table 1 Baseline Characteristics of Patients

Variables		C-Group[a] (N=14)	IC-Group[b] (N=7)	P-value
Gender	Male Female	10 4	7 0	0.11
Age	≤60 >60	5 9	1 6	0.31
ECOG	0 1	3 11	1 6	0.69
HAS	yes no	10 4	3 4	0.2
Serum AFP (ng/mL)	>20 ≤20	12 2	7 0	0.29
Lauren classification	Intestinal Mixed Diffuse	8 3 3	2 1 4	0.37
Her-2 amplification	positive negative	3 11	0 7	0.19
Location of tumor	GEJ Stomach	5 9	1 6	0.31
Liver metastasis	yes no	11 3	6 1	0.69
CPS	<1 ≥1	10 4	1 6	0.01

Notes: [a]C-group, control group. [b]IC-group, immunotherapy group.

anti-angiogenic therapy). Three patients received second-line treatment in the immunotherapy group (2 chemotherapy and 1 anti-angiogenic therapy).

The mOS of the control group was 16.0 months (14 months in chemotherapy alone subgroup, and 20.0 months in subgroup receiving chemotherapy plus apatinib or Herceptin), while the mOS of immunotherapy group was not reached (Figure 3B, P=0.03).

In the immunotherapy group, main immune-related adverse effects were skin rash (6/7), hypothyroidism (3/7), hypophysitis (2/7), diarrhea (1/7). There were 4 adverse events above grade 3, including hypophysitis twice, immune-related diarrhea once and skin rash once, which could be recovered after active treatment. One patient developed non-obstructive jaundice, which was ineffective with hormone therapy. The CT scan showed rapid progression. Jaundice was disappeared after second-line antineoplastic therapy (apatinib), considering that jaundice may be related to disease progression instead of side effects of immunotherapy.

The results indicated the effect of immunotherapy in the first-line treatment of HAS/AFPGC.

Table 2 Comparison of Objective Response Rates to Different Treatment Regimens

	Control Group (n=14)	Immunotherapy Group (n=7)
CR	0 (0)	1 (14.3%)
PR	3 (21.4%)	5 (71.4%)
SD	8 (57.1%)	0 (0)
PD	3 (21.4%)	1 (14.3%)

Discussion

As a specific tumor marker, AFP is a glycoprotein produced by fetal liver, yolk sac and fetal gastrointestinal cells and is widely used in the diagnosis of HCC and yolk cyst tumors.[15] Recently, studies have shown that other human tumors (such as gastric cancer, colorectal cancer, gallbladder cancer, lung cancer and ovarian cancer) can also lead to an increase of serum AFP, of which gastric cancer is the most common one.[16] AFPGC is defined as gastric cancer with elevated serum AFP. In clinical, some gastric cancer patients with liver metastasis or chronic hepatitis B will also have elevated serum AFP. Therefore, a cutoff value of AFP (20 ng/mL or 40 ng/mL) is set in clinical studies.[17–20] Previous studies have shown that in patients with elevated serum AFP, the positive rate of immunohistochemistry AFP is 64.493.7%.[2,7] The diagnostic basis of HAS is uncertain, which is often defined as a component of the morphological differentiation of "hepatocellular carcinoma (HCC) like differentiation" in primary gastric cancer.[21–23] Some studies have shown that such differentiation also exists in liver and lymph node metastases[7,24] However, serum AFP is not elevated in all HAS. The positive rate of serum AFP in HAS is 5487%,[21,22] which is consistent with our study. In a word, the concepts of AFPGC and HAS have both intersection and difference. In fact, AFPGC and HAS represent some special types of gastric cancer from the perspective of clinical phenomena and pathomorphology, while the current diagnostic criteria in clinical need to be further improved.

The marked clinical features of AFPGC/HAS are high invasiveness, early metastasis, and rapid progress. The long-term follow-up results of 104 patients with AFPGC showed that the incidence of liver metastasis was 60.6%, with a median time of 7.4 months from the detection of liver metastasis to surgery, which is far shorter than that

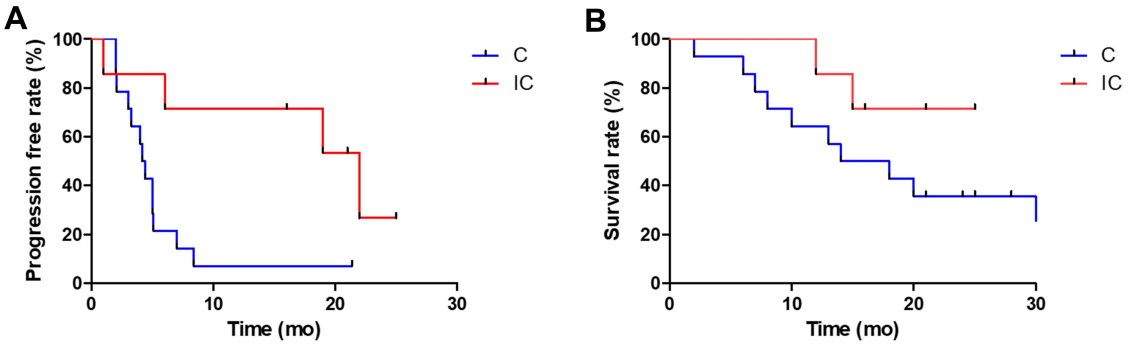

Figure 3 Comparison of progress-free survival (**A**) and overall survival (**B**) of AFPGC/HAS patients treated with chemotherapy and those receiving immunotherapy plus chemotherapy.
Abbreviations: C, chemotherapy; IC, immunotherapy plus chemotherapy.

(20.6 months) of common gastric adenocarcinoma.[7] Yang et al showed that the incidence of lymph node metastasis and liver metastasis was 77.4% and 41.9%, respectively, in a follow-up study of 31 patients with HAS.[8] In fact, due to the high degree of malignancy and rapid disease progress of AFPGC/HAS, most patients miss the opportunity for surgery at the time of diagnosis. Therefore, these clinical studies for postoperative patients are not enough to summarize the overall characteristics of such patients and guide the clinical practice.

However, for patients with advanced AFPGC/HAS, there are few reports and lack of special treatment at present. In 2019, Zhang et al reported the efficacy of different chemotherapy regimens in 105 patients with advanced AFPGC. Intensive treatment (triplet regimen) seems to have slightly better disease control rate with 13.9 months of median OS.[25]

We investigated the application of immunotherapy plus chemotherapy in advanced AFPGC/HAS in this study. We observed an encouraging curative effect, and some patients showed the tail effect with long-term disease control time. Because of the small sample size, it is difficult to analyze the efficacy-related predictors. As this is a real-world study, the expression of PD-L1 was not balanced between the two groups. In the immunotherapy group, however, one patient with high expression of PD-L1 exhibited hyperprogressive disease (HRD), and another patient with PD-L1 negative obtained PR. It seems that the efficacy of combined therapy cannot be predicted simply by PD-L1 expression (Table 3). In the second-line treatment, 3 patients tried PD1 combined chemotherapy among the patients failed with first-line chemotherapy. However, all three patients had the disease control time less than 3 months. It suggests that the therapeutic effect of second-line immunotherapy is not good, which may be related to physical condition and disease load of the patients.

Notably, one patient treated with chemotherapy plus anti-angiogenic drug reached PR with PFS for more than 13 months in the first-line treatment. In the control group, two out of three patients who were treated with apatinib after the failure of first-line chemotherapy showed good response, one with PFS for more than 12 months and the other for 7 months. The third one had PFS for 3 months. In the immunotherapy group, one patient's disease was controlled by apatinib after HRD. This suggests that antiangiogenic treatment may also be an option. It is consistent with previous case reports on the efficacy of antiangiogenic therapy in AFPGC.[26,27]

AFPGC/HAS patients respond to immunotherapy, possibly associated with their specific genetic features. Recent studies suggest that most TCGA tumors with elevated AFP expression were categorized as CIN subtypes.[28] Loss of heterozygosity (LOH) occurs frequently in gastric cancer, resulting in chromosomal instability and loss of tumor suppressor genes. The degree of LOH in AFPGC was high, including 17p (100%), 13q (88%), 3P (87%), 5q and 9p (80%), 11q (70%), 18q (58%), 16q (53%) and 8p (50%), and the median index of

Table 3 The Treatment of Immune Therapy Group and Evaluation of Effectiveness

No.	CPS	Efficacy	PFS (Month)
13	1	PR	19
14	<1	PR	6
15	1	CR	22
16	1	PR	NR[a] (>21 months)
17	1	PR	NR[a] (>25 months)
18	1	PR	NR[a] (>16 months)
20	10	PD	1

Abbreviation: [a]NR, not reached

allele loss was 72%, which is much higher than about 50% of normal gastric adenocarcinoma. Some scholars speculate that the silencing of a key gene on chromosome 13q or 18q promotes the development of HAS,[29–31] leading to high tumor mutational burden (TMB), which could explain why AFPGC/HAS patients responded to immunotherapy from one aspect. Due to the lack of pathological tissues, NGS tests were not conducted in this study, so whether this conclusion is valid still needs further investigation.

Conclusion

This study suggests that immunotherapy plus chemotherapy can be used as a treatment option for AFPGC/HAS. Further investigation on the immunotherapy of AFGC/HAS patients is warranted.

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Disclosure

The authors report no conflicts of interest in this work.

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