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Literature Review of Gastric Cancer Producing Alpha-fetoprotein

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Abstract

Background: Gastric cancer is the third most common cause of cancer-related death worldwide. Alpha-fetoprotein producing gastric cancer (AFP-GC) is a subtype of gastric cancer which has more aggressive behavior than the common type. Awareness and understanding of this disease entity are of paramount importance, because treatment is different from that of the classical gastric cancer.

Method: The literature search started from 1970, when the first patient of AFP-GC was reported, until March of 2017, using Google search engine, PUB Med to identify relevant articles on alpha-fetoprotein producing gastric cancer. Subsequent references searches were done from the retrieved articles.

Results: Since the first case of alpha-fetoprotein producing gastric cancer was first reported, many cases have been reported, mostly in Asia. Although AFP-GCs have been recognized in Japan and parts of Asia for more than 40 years, there were only a few publications about AFP-GC outside of Asia. In this article, I review literature concerning the clinicopathological features, immunoreactivity, molecular biology, treatment, and prognosis of AFP-GC.

Conclusion: In the literature, some potential protein markers were identified, and cellular pathways involved in AFP-GCs were suggested. Two types of targeted drugs have been used to treat such patients with a good response. Further studies of the roles of these markers and pathways may shed light on developing more effective drugs to treat patients with AFP-GC.

Keywords: Alpha-fetoprotein; Gastric cancer; Chemotherapy; Targeted therapy; Liver metastasis; Molecular biology; Immunoreactivity; HER2; Prognosis

Abbreviations

AFP: alpha-fetoprotein; AFP-GC: Alpha-fetoprotein Producing Gastric Cancer; HCC: Hepatocellular Carcinoma; IHC: Immunohistochemistry; SALL 4: Sal-like Protein 4; HNF1: Hepatocyte Nuclear Factor 1; ATBF1: AT Motif Binding Factor 1; VEGF: Vascular Endothelial Growth Factor; XIAP: X-linked Inhibitor of Apoptosis; IGFIrβ: Insulin-like Growth Factor-I receptor β; STAT3: Signal Transducer and Activator of Transcription 3; RFS: Relapse Free Survival; CI: Confidence Interval; FDA: Food Drug Administration; VEGFR :Vascular Endothelial Growth Factor Receptor; HR2: Human Epidermal Growth Factor.

Introduction

Alpha-fetoprotein (AFP) is an albumin-like glycoprotein with a molecular weight of 70,00 Daltons, first identified in the human fetus in 1956 [1]. It is produced by yolk sac cells, fetal hepatic cells and some gastrointestinal cells [2]. It is a major component of fetal plasma, reaching a peak concentration of 3mg/ml at 12 weeks of gestation. Following birth, it clears rapidly from the circulation, having a half life of 3.5 days, and its concentration in adult serum is less than 20ng/ml. Elevated serum Levels of AFP were initially used for screening and monitoring hepatocellular carcinoma (HCC) [3]. Later, high serum levels of AFP were found in many other malignant neoplasms including the primary site in the lung, ovary, stomach, urinary tract and the germ cell tumors such as yolk sac tumor in the testis and the mediastinum [4-8]; of which, the gastric cancer is the most common [9]. Concentrations of AFP above the reference range also have been found in serum of patients with benign liver disease (e.g. viral hepatitis, cirrhosis), neural tubal defects and in ataxia telangiectasia [10]. Serum AFP level is elevated during pregnancy, reaching a peak level during the third trimester; persistent elevation of serum level of AFP in the mother following birth is a rare hereditary condition [11].

Method

The literature search started from 1970, when the first patient of AFP-GC was reported, until March of 2017, using Google search engine, PUB Med to identify pertinent articles on alpha-fetoprotein producing gastric cancer. Subsequent references searches were done from the retrieved articles.

Results

Incidence

Since the first case of AFP producing gastric cancer (AFP-GC) was reported [9], many cases have been reported in Asia. The reported incidence was 6.63% in China [12], and 1.5 -3% in Japan [13] respectively. Huang and Tsung reported the first case of AFP-

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GC in Taiwan, [14]; later more cases were reported [15,16]. The true incidence of AFP-GC in Taiwan still remains unknown. Although AFP-GCs have been recognized in Japan and parts of Asia for more than 40 years, there are few publications about AFP-GCs outside of Asia [17-20].

Clinicopathological characteristics of AFP-GC

Comparison of clinicopathologic characteristics between AFP positive and negative groups showed that there were no significant differences in gender, age distribution, tumor location, and degree of differentiation Gastric cancers, like other cancers showed significant heterogeneity histologically, clinically and genetically. AFP-GC is a subtype of gastric cancer. In the literature, most studies showed significant difference in the number of lymph node metastasis, the maximal tumor diameter, pathological stage, vascular invasion, survival time and liver metastasis between the AFP positive group and negative group [16,21-23]. AFP-GC phenotype can be classified into hepatoid adenocarcinoma, intestinal and signet ring type. AFP producing activity was mostly found in the hepatoid type, but also could be found in the intestinal type as well as in the signet ring type. The hepatoid type is a special type of gastric carcinoma which has a striking morphological similarity to HCC [24].

The characteristics of immunoreactivity

Many studies have been performed on the immunoreactivity of alpha-fetoprotein producing gastric cancer [24-26]. It seemed that the tumor tissue from AFP-GC expressed the same reactivity with that from HCC using the same antibodies when immunohistochemical (IHC) stainings were performed. It was shown recently that CD10 was expressed in normal hepatic tissue as well as in HCC tumor tissue. Thus, CD10 may serve as an additional marker for hepatic differentiation [27]: In the literature, only two cases of AFP-GC tumor tissue were studied for CD10 expression which was negative. In a study by Tsung, [28] none of 6 cases showed CD10 expression. CD10 might be used to differentiate HCC from AFP-GC. In addition, two more markers, SALL 4(Sal-like protein 4) and Glypican 3, could potentially useful for this purpose [29,30]; however, a larger number of study is required to confirm this observation. In some reported cases of AFP-GC [23,28,31,32], the immunoreactivity for AFP was negative using anti-AFP. The reason could be related to its sensitivity. In two cases, the patients' serum levels of AFP were 46.49 ng/ml and 23.83ng/ml respectively [31,32]. In the study by Tsung [28], immunoreactivity for AFP was demonstrated in 5 of 6 AFP-GCs. The patient with signet ring cell type had AFP serum level of 23,041ng/ml; sensitivity should not have been the issue. Another explanation could be due to the limited sampling [25]. A recent study by Kinjio et al. [33], suggested that the gastric carcinoma starts on the mucosa, which differentiated into enteroblastic type and hepatoid type. During the process of tumor invasion and proliferation, the tumor cells acquired the AFP production ability. Therefore, the tumor cells from the surface might be negative for the AFP reactivity.

Molecular biology of AFP-GC

AFP-GC is very malignant and highly metastatic compared with common gastric cancer. However, the causal relationship between AFP production and the high malignancy of AFP-GC is still unclear. Hiromi et al. [34], investigated AFP gene regulation in AFP-GC by an active transcription factor, HNF1 (hepatocyte nuclear factor 1) and a repressive transcription factor, ATBF1 (AT motif binding factor 1).Using RNase protection assays, they demonstrated that the production of AFP in gastric cancer cells did not directly associate with HNF1 expression. An inverse relation between the expressions of ATBF1 and AFP was clearly observed in gastric cancer cells. Immunohistochemistry of resected clinical samples revealed that AFP producing cells lacked ATBF1 immunoreactivity. Their data suggests that the absence of ATBF1 was responsible for AFP gene expression in gastric cancer. Therefore, the absence of ATBF1 was a distinct characteristic of AFP-GC and might be important for its highly malignant nature.

An early report indicated that AFP had suppressive effect on lymphocyte transformation [35]. Another report [36] indicated that AFP could enhance proliferative activity and increased angiogenesis due to positive expression of vascular endothelial growth factor (VEGF). In a study in 2000, it was found that hepatocyte growth factor (HGF) and c-met expression in AFP-GC was higher than that in AFP negative gastric cancer. Through the HGF and c-met pathway, AFP promoted tumor growth [37].

He et al, [38] using the protein pathway array, 11 of out of 286 proteins tested were found to be differentially expressed, and several of them correlated with prognosis of AFP producing gastric adenocarcinoma. Two of them were worth mentioning; XIAP (X-linked inhibitor of apoptosis) and IGFIrβ (Insulin-like growth factor-I receptor β). Previous studies demonstrated that XIAP is up-regulated in many gastric adenocarcinoma cells [39,40] and XIAP inhibitors could increase apoptosis and enhanced sensitivity of gastric adenocarcinoma cell lines to chemotherapy [41–43]. Therefore, XIAP was considered as a potential target for gastric adenocarcinoma therapy [44]. It was shown that the suppression of IGF-Ir caused apoptosis and reduced proliferation of gastric adenocarcinoma cells [45,46]. High level expression of IGF-Ir promoted tumor growth and metastasis in gastric adenocarcinoma. It was known that signal transducer and activator of transcription 3 (STAT3) had an important role in tumorigenesis of various primary cancers and cancer cells by upregulating cell–survival and downregulating tumor suppressor protein [47]. In an experiment, Jia et al. using arsenic trioxide to induce apoptosis on AFP-GC cells, they found decreased expression of AFP and STAT3. Downregulation of AFP and STAT3 expression might play an important role in arsenic trioxide induced apoptosis of AFP-GC cells, which suggested a new mechanism of arsenic trioxide cell induced apoptosis. Arsenic trioxide might be a possible agent to treat AFP-GC [48].

Treatment of AFP-GC

No standard therapy is currently available. However, radical surgery and chemoradiation therapy may positively impact clinical outcomes. AFP-GC with liver metastasis has a particularly dismal prognosis, regardless of whether it is synchronous or metachronus. Previous studies showed that 5-year survival rate and median survival times were 0-3.8% and 9-11.4 months, respectively [21,49]. In the literature, an alpha-fetoprotein-producing cancer patient with multiple liver metastases was successfully treated with paclitaxel-based chemotherapy [50]. Since FDA approved targeted therapies for advanced gastric cancer and cancer arising from gastroesophgageal junction on October 20, 2010, reports improving prognosis using

targeted therapies for advanced gastric cancer have appeared in the literature [50,51]. Subsequently, reports of improving prognosis or prolonged survival on AFP-GCs patients treated with trastuzumab followed [52,53]. Trastuzumab (Herceptin) is a monoclonal antibody of a very specific immune system protein, which targets the HER2 protein. Giving trastuzumab with chemotherapy could help patients with advanced HER2-positive cancer live longer than giving chemotherapy alone [54]. Therefore, assessment of HER2 status is now mandatory for selecting patients' eligibility for this treatment [55].

The other drug is called ramucirumab, which is a monoclonal antibody, an antagonist to VEGFR (Vascular Endothelial Growth Factor Receptor). Specifically, this drug targets VEGFR, blocking the growth of new blood vessels in the tumor that are needed for the tumor to grow and spread. To the best of my knowledge, there was one report on a patient with AFP-G treated with this type of drug [56]. The treatment kept her progression –free survival for 5 months, and the overall survival was 4.5 years.

Prognosis

The prognosis of AFP-producing gastric cancer was reported to be poor. One study reported that the 1-, 3- and 5-year survival rates of AFP-producing gastric cancer were 53%, 35% and 28%, respectively [57]. Another reported the 5-year survival rate of AFP positive gastric cancer to be 28.4% [22]. However, the related literature described some different observation. Chun et al. [21] reported the 5-year survival rate of the AFP positive group to be 66% vs 80% of AFP negative group. Taking into consideration of the serum level of AFP, Lin et al. [16] found that 1-,3-,5-, and 10-year survival rates for AFP<300ng/ml patients were 46.7%, 28.9%,17.8%, and 13.3% respectively. The 1-,3-,5-year survival rates for AFP>300ng/ml were 15.4%, 7.7%, and 0% respectively. In three studies [21,23,38,57], multivariate survival analysis revealed that AFP positivity to be the independent prognostic factor. In the study by Liang et.al.(38), in AFP producing gastric adenocarcinoma group, 27 patients had relapsed [84.4% (27/32)] compared with 28 in AFP nonproducing gastric adenocarcinoma group [62.2% (28/45)]. Mean relapse free survival (RFS) was 9 months (95%CI: 6.6-11.6 months) in the AFP producing gastric adenocarcinoma group, compared with 30 months (95% CI: 6.6-53.4 months) in the AFP non-producing gastric adenocarcinoma group. In AFP producing gastric adenocarcinoma group, 20 patients had liver metastasis [62.5% (20/32)] compared with 5 in AFP non-producing gastric adenocarcinoma group results [11.1% (5/45)]. However, there has been some controversy about the link between AFP and survival duration [58-60]. Inoue and colleagues [58] observed that one patient with high serum AFP (25,400ng/ml) was still living 12 year after diagnosis of gastric cancer. This might be an isolated case.

Conclusion

AFP-GC is a special subtype of gastric carcinoma that is associated with aggressive behavior and poor prognosis. No standard therapy is currently available. Radical surgery and chemoradiation therapy seldom offer positive clinical outcomes. Elevation of serum AFP may contribute to its aggressive behavior. Although, the underlined mechanisms are not completely understood; some potential protein markers were identified and cellular pathways involved in AFP-GC were suggested. I feel that chemotherapy combined with targeted therapy can lead to a better prognosis. Some case reports in the literature seem to support this concept. However, a large cohort is needed to validate these reports. Furthermore, more basic studies of the roles of these markers and pathways are justified, hoping that more effective drugs will be developed.

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