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New Perspectives of Epstein–Barr Virus-Associated Gastric Cancer

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Abstract

Gastric cancer (CG) is one of the most common neoplasms in Peru. Recently the molecular subtypes have been typified in CG. A molecular subtype is associated with the Epstein Barr virus. This entity presents with a frequency of 10%, in a non-cardiac region, in male patients and with the intestinal histological subtype. The prognosis is better compared to the other types of CG. It presents its own molecular alterations that in the future could be susceptible to target therapies and immunotherapy.

Introduction

Gastric cancer (GC) is the fifth most frequent cancer in the world [1]. The incidence of CG mortality is declining due to the eradication of Helicobacter pylori and screening [2]. However, cardiac adenocarcinoma is increasing in the USA and Europe [3,4]. Most cases are diagnosed in advanced stages therefore a poor prognosis. CG is multifactorial, with complex genetic and environmental interactions. Lauren's classification is divided into two histological types: diffuse and intestinal [5]. However, in 2014, Cancer Genome Atlas (TCGA) Research Network published genomic profiling of gastric adenocarcinomas and four genomic subtypes were defined: microsatellite instability (MSI+) (22%), Epstein Barr Virus infection (EBV+) (9%), genomic stability with low degree of aneuploidy (GS) (20%), and tumors exhibiting chromosomal instability with high degree of aneuploidy (CIN) (50%) [6].

In 2015, the Asian Cancer Research Group (ACRG) reported four subtypes: microsatellite instability (MSI) (23%), tumors that are microsatellite stable and TP53 mutation-negative (MSS/TP53−) (36%), tumors that are microsatellite stable and TP53 mutation positive (MSS/TP53+) (26%) that includes EBV + Gastric Cancer (EBV GC), and tumors that are microsatellite stable and exhibit features of epithelial to mesenchymal transition (MSS/EMT) (15%) [7]. EBV GC emerges as a new subtype of gastric cancer with molecular and clinicopathological characteristics and potential targeted treatment .

Pathogenesis

Epstein-Barr virus (EBV) causes 10% GC (range 2% –20%) [8]. EBV CG is associated with extensive hypermethylation of DNA [9]. Methylation of host cell DNA inactivated tumor suppressor genes and tumor-associated antigens [10]. EBV latent membrane protein 2A (LMP2A) activates transcription of DNA methyltransferase 1 for phosphorylation of STAT3 [11]. TET2 downregulation is crucial in inducing DNA methylation in EBV GC. [12]. LMP2A inducing the phosphorylation of ERK, might lead to the overexpression of DNMT3a. DNMT3a may further cause the hypermethylation of the AQP3 gene [13]. EBV miRNAs are associated with cell adhesion, signal transduction and apoptosis [14]. ARID1A and BCOR mutations are frequent in this entity [15,16]. 80% of patients with positive EBV CG present mutations in PIK3CA and amplification of JAK2, CD274, and PDCD1LG2; the latter codes for PDL1 and PD-L2 [15]. EBV can in association with Helicobacter pylori generate a synergism in the carcinogenesis of this entity [16,17].

Clinical Features

This entity has a predominance of men, which is confirmed in several studies [18,19]. Smoking was reported as a condition related to EBV CG (20y). Gastric remnant cancer after distal gastrectomy can be associated with EBV [21,22]. The most frequent location is in the upper or middle third of the stomach [23]. Also, it shows lower T and N compared to EBV negative GC [24,25]. The histological type is controversial, however recent studies show that they mostly correspond to the intestinal type [26]. Viral loads correlate with upregulation of PD-L1 and worse prognosis in EBV GC [27].

Prognosis

The prognostic role of EBV in CG is controversial. However, a study involving thirteen publications with 4,599 patients, suggests that EBV associated with the CG presents a better

prognosis with a reduction of the relative risk of death of 28% [28]. Evidence suggests better survival for EBV GC only in Asian populations [29]. An explanation for a favorable prognosis of the disease would be related to the immune response present, as seen with histological types of EBV such as lymphoepithelioma-like form and Crohn-like but not in the adenocarcinoma subtype [30,31].

Treatment

Two studies not showed benefit of adjuvant chemotherapy in EBV CG [32,33]. For metastatic scenary could have future some interesting options:

i. Nivolumab and pembrolizumab are anti PD1, check point inhibitors approval for the treatment of GC advanced [34,35]. EBV GC display PD-L1/2 overexpression and occasional immune cell signaling activation [36,37]. A recent study showed that high levels of tumor-infiltrating lymphocytes are related to favorable prognosis and intratumoral PD-L1 with a worse prognosis in EBV CG [38,39]. Kim et al. [40] demonstrated ORR 100% in EBV GC with pembrolizumab. PDL1 is a prognostic and predictive biomarker in EBV CG and check point inhibitor could be an excellent options therapeutics in EBV CG.

ii. PIK3CA mutations are considered a key parameter in EBV CG but prognostic status is controversial [41-43]. Different inhibitors to block the effect of the PI3K/AKT/mTOR pathway are currently under investigation.

iii. Hypermethylation is a fundamental for the development and progression of EBV CG [44-47]. Treatment with DNA demethylating agents could be important for this entity [48]. A study reported that low concentrations of demethylating agents, as 5-azacitidine or trichostatin A, induced the expression of EBV lytic genes, such as BMRF1, BZLF1, and BRLF1, in EBV GC cell lines [49]. Lytic EBV infection can induce the lysis of tumor cells [50-52]. New studies with demethylating agents are necessary or agents that can induce EBV lytic phase.

Conclusion

In conclusion, EBV GC has molecular characteristics, own clinics and forecasts. Coinfection with Helicobacter pilori seems to be a pathway of carcinogenesis of this entity. Check point inhibitor , inhibitors of PI3K/AKT/mTOR pathway and demethylating agents, are drugs that emerging for the treatment of this disease. It is necessary to define prognostic biomarkers to stablish a real precision medicine for this disease.

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