



A New Paradigm in the Treatment of Gastric Cancer

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Abstract

Gastric Cancer (GC) is the fourth common cancer worldwide. It has a geographical distribution affecting mainly the developing countries much more than the developed ones. It is an aggressive disease with poor outcome. Little breakthroughs were achieved in the treatment of GC in the last few decades. These were confined to chemotherapy and surgical techniques. The development of gastric cancer is a complex, multistep process, which involves multiple genetic and epigenetic alterations. The previous classifications of GC had limited impact on its management and prognosis. A novel molecular classification will enhance our understanding of the cancer of the stomach and it will individualize our therapy in a targeted manner for more robust results and better prognosis.

According to The Cancer Genome Atlas Project (TCGA), GC has been recently divided into 4 categories according to the molecular imprint specification. These 4 subtypes are Epstein-Barr virus positive tumors (EBVp), microsatellite instability tumors (MSI), genomically stable tumors (GS) and tumors with chromosomal instability (CIN). There is an immense diversity in the pathways where targeted and immunotherapeutic agents could treat gastric cancer. We propose a possible new treatment approach against gastric cancer guided by its genetic fingerprint.

Keywords: Gastric cancer; Treatment; Classification; Genomic mapping

Abbreviation: GC: Gastric Cancer; TCGA: The Cancer Genome Atlas Project; GS: Genomically Stable Tumors; MSI: Microsatellite Instability Tumors; EBVp: Epstein - Barr virus Positive Tumors; CIN: Chromosomal Instability; EBVpGC: Epstein-Barr Virus Positive Gastric Cancer; CpG: 5'Cytosine—Phosphate—Guanine3'; LMP2A: The Latent Membrane Protein 2A; DNA: Deoxyribonucleic Acid; DNMT1: DNA Methyltransferase 1; CDKN2A: Cyclin-Dependent Kinase Inhibitor 2A; MLH1: MutL Homolog 1; PI3K CA: Phosphatidylinositol-4,5-Bisphosphate 3-Kinase, Catalytic Subunit Alpha; ARID1A: AT-Rich Interactive Domain 1A; BCOR: BCL6 Corepressor; JAK2: Janus Kinase 2; PD-L1/2: Programmed Cell Death 1 Ligand and 2; mTOR: Mammalian Target of Rapamycin; PKB: Protein Kinase B; MHC I: Major Histocompatibility Complex Class I Gene; HER: Human Epidermal Growth Factor Receptor; EGFR: Epidermal Growth Factor Receptor; CCNE1: Cyclin E1; CCND1: Cyclin D1; CDK6: Cyclin-Dependent Kinase 6; MET: Mesenchymal Epithelial Transition Factor; FGFR: Fibroblast Growth Factor Receptor; VEGFA: Vascular Endothelial Growth Factor A; RHOA: ras Homolog Family Member A; CDH1: Cadherin 1; CLDN18: Claudin 18; ARHGAP26: Rho GTPase-Activating Protein 6

Introduction

Gastric cancer (GC) was the fourth most common type of cancer and the third leading cause of cancer-related death worldwide in 2012 [1]. It has a greater incidence among the developing countries which is attributed to the different preventive health measures carried out by their developed counterparts [1]. In the United States, it represents only 1,6% of all cancers [2]. For the past few decades, clinicians used mainly Lauren's classification of GC in their practice, where GC is divided into 2 main types, intestinal and diffuse [3]. Both types have almost similar lifestyle and environmental risk factors but the latter exhibits more a genetic foundation. But this classification has limited clinical value with little effect on the course of therapy.

With the modern advances in molecular profiling, it is possible now to have a better understanding of the genetic pathophysiology of primary gastric carcinoma. Molecular profiling would shape a more comprehensive vision on the optimal classification in order to tailor well individualized therapies for GC patients [4,5]. In this regard, The Cancer Genome Atlas Project (TCGA) developed a novel genomic classification of GC. They divided GC into four different genomic tumors: Epstein-Barr virus (EBV) positive tumors (EBVp), microsatellite instability tumors (MSI), genomically stable tumors (GS) and tumors with chromosomal instability (CIN) [4,6]. These 4 subtypes have such distinctive genetic features that they might be considered as totally separate entities.

The first group of tumors is Epstein-Barr virus positive gastric cancer (EBVpGC) [4]. EBV positivity, which represents 9% of the cases, is a good prognostic factor in resected GC [4,7]. The chief molecular signature of this group is 5'Cytosine—phosphate—Guanine3' (CpG) island promoter methylation of GC related genes [8]. The latent membrane protein 2A (LMP2A) expression of EBV may promote Deoxyribonucleic acid (DNA) methylation through inducing signal transducer and activator of transcription 3 (STAT3) phosphorylation and subsequent transcription of DNA methyltransferase 1 (DNMT1) [9]. DNA hypermethylations are greatly upregulated in EBVpGCs compared to the other groups. Both promoter and non-promoter CpG islands are expressed in EBV-associated DNA hypermethylations.

Interestingly, Cyclin-dependent kinase inhibitor 2A (CDKN2A) promoter hypermethylation was displayed in all EBVpGCs, while mutL homolog 1 (MLH1) hypermethylation was not recorded [4]. On the other hand, there is a clear expression of the phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (PI3K CA) mutation in EBVpGCs; in addition, 55% had AT-rich interactive domain 1A (ARID1A) mutation and 23 % had the BCL6 corepressor (BCOR) mutation, but they have hardly ever shown a TP53 mutation. Moreover, multiple new amplification locus for janus kinase 2 (JAK2), CD274, and programmed cell death 1 ligand and 2 (PD-L1/2) were detected repeatedly in EBVpGCs. JAK2 is used by several class I cytokine receptor to activate STAT to regulate gene transcription. As for PD-L1/2 and their receptors PD-1/2, they are involved in immune checkpoints [4,6].

From the above TCGA findings, many potential therapeutic pathways have been made possible to target EBVpGC. The novel therapies should be directed against the high expression of PD-L1 and PD-L2, JAK2 amplification and PI3K CA mutation either by direct inhibition, or alternative mechanism through mammalian Target of Rapamycin (mTOR) and Protein kinase B (PKB) [10]. Promising results are yet awaited to emerge from the clinical trials involving the checkpoint inhibitors. The second category is the MSI GC. It forms 21 % of all GCs with positive prognostic marker in resected GCs [10,11]. MSI is recognised as an early event in GC tumorigenesis [12]. It is caused by extensive replication errors in simple repetitive microsatellite sequences due to the defects in mismatch repair genes, mainly in the major histocompatibility complex class I gene (MHC I).

According to TCGA, MSI subtype was characterized by accumulation of different mutations in *PIK3CA*, human epidermal growth factor receptor (HER) 3, *HER2*, and epidermal growth factor receptor (*EGFR*), with an increase in the numbers of tumor specific neoantigens [6]. The favorable targetable pathways for this group are immunotherapy which is related to the elevated numbers of tumor specific neoantigens and MHC class I aberrations, drugs directed against HER3, Kirsten rat sarcoma viral oncogene homolog (*KRAS*), *HER2*, *EGFR* and *PIK3CA* mutation either by direct inhibition or alternative

mechanism through mTOR and PKB [10]. Trastuzumab, an HER2 monoclonal antibody, is one example where it showed better overall survival when it was combined with chemotherapy in patients with HER2 over expressed metastatic GC [13].

The third group is CIN and it is the largest making 50% of all GCs. CIN is due to the imbalanced division of chromosomes to daughter cells upon mitosis and results in the loss or gain of DNA during cell division [14]. Copy number gains at 8q, 12q, 13q, 17q, and 20q and copy number losses at 3p, 4q, 5q, 15q, 16q, and 17q are frequently noted in GCs [15-18]. CIN is involved in focal gene amplifications as well as to chromosomal gains and losses. The main findings in CIN were genomic amplifications of genes that encode receptor tyrosine kinases (RTK), elevated phosphorylation of EGFR which consistent with amplification of *EGFR*, and amplifications of cell cycle genes Cyclin E1 (*CCNE1*), Cyclin D1 (*CCND1*), and Cyclin-dependent kinase 6 (*CDK6*) [4,6].

The CIN subtype was studied abundantly in clinical trials over the past decade due to the numerous available targetable pathways. The majority of agents are aimed at the RTK gene amplifications, including HER2, EGFR, mesenchymal epithelial transition factor (MET), fibroblast growth factor receptor (FGFR) and vascular endothelial growth factor A (VEGFA) [10]. Ramucirumab, a human VEGF receptor 2 antagonist, has shown significant improvement in overall survival in patients with recurrent or progressive gastric and gastro-esophageal junction cancer after primary treatment with platinum or fluoropyrimidine combination chemotherapy, either as a single agent or in combination with paclitaxel [19].

The Authors of TCGA describe a fourth group which is the GS tumors. It constitutes 20% of GCs [10]. This group has an upregulated ras homolog family member A (RHOA) mutation in 15% of the cases. The role of RHOA in cell motility points out the contribution of RHOA modification to altered cell adhesion in the carcinogenesis of GCs. Interestingly, they found mutations in cadherin 1 (CDH1) which underlie a hereditary pattern with an inferior outcome. Other genetic abnormalities have been noted such as a recurrent interchromosomal translocation between claudin 18 (CLDN18) and Rho GTPase-activating protein 6 (ARHGAP26) [6]. As such, many therapeutic options can be studied in this subtype to target different promising pathways such as the RHOA dysregulation, FGFR, VEGF-A and *PIK3CA* mutation by either direct inhibition, or alternative mechanism through mTOR and PKB [10]. Many agents are currently under clinical phase I and II trials with little evidence yet to show.

It is worth noting that outside the new TCGA classification, angiogenesis stands almost alone as a plausible target. With much evidence, the high manifestation of the proangiogenic VEGF was associated with an inferior overall survival in gastric cancer patients. VEGF-A was seen as a major indicator of the risk of bone marrow metastasis, while VEGF-D is considered as a valuable predictor of the lymphatic metastasis in gastric

cancer patients. It would be vital to recognize the expression of the different VEGF family members in the primary GC tumor in order to establish the risk of distant metastasis and the benefit of anti-VEGF therapy [20-21].

Conclusion

Despite the advances in molecular genomics in the recent years, the exact mechanisms underlying gastric cancer tumorigenesis are still not yet completely reached. The necessity to overcome its aggressive nature and its dim outcome is of utmost importance by means of novel treatment options. TCGA has offered a new molecular classification of GC that paved the way to a more explicit categorization of the different genotypic entities of GC. The findings would delineate a road map for the many potential specific targeted pathways for the treatment of GC. A few drugs have shown good evidence in treating GC, but we are far behind attaining a cure in the metastatic setting. While the basis of the development of GC is complex and multifactorial, our therapy should be a combination of different targeted or immunotherapeutic agents designed by using the most recent genomic backbone of GC tumors.

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