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TOPIC HIGHLIGHT

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Novel findings about management of gastric cancer: A summary from 10th IGCC

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Abstract

The Tenth International Gastric Cancer Congress (IGCC) was held in Verona, Italy, from June 19 to 22, 2013. The meeting enclosed various aspects of stomach tumor management, including both tightly clinical approaches, and topics more related to basic research. Moreover, an overview on gastrointestinal stromal tumors was provided too, although here not discussed. Here we will discuss some topics related to molecular biology of gastric cancer (GC), inherent to prognostic, diagnostic and therapeutic tools shown at the conference. Results about well known subjects, such as E-cadherin loss of expression/function, were presented. They revealed that other mutations of the gene were identified, showing a continuous research to improve diagnosis and prognosis of stomach tumor. Simultaneously, new possible molecular markers with an established role for other neoplasms, were discussed, such as mesothelin, stomatin-like protein 2 and Notch-1. Hence, a wide overview including both old and new diagnostic/prognostic tools was offered. Great attention was also dedicated to possible drugs to be used against GC. They included monoclonal antibodies, such as MS57-2.1, drugs used in other pathologies, such as maraviroc, and natural extracts from plants such as biflorin. We would like to contribute to summarize the most impressive studies presented at the IGCC, concerning novel findings about molecular biology of gastric cancer. Although further investigations will be necessary, it can be inferred that more and more tools were developed, so as to better face stomach neoplasms.

Key words: Gastric cancer; Prognostic tools; Markers; Therapy

Core tip: Gastric cancer (GC) is one of the most common tumors in the world, although scientists' knowledge about this neoplasm grew in the last years. In June, an international meeting (10th International Gastric Cancer Congress), focused on GC management, was held in Verona (Italy). It gave an overview about the state-of-the-art stomach tumor treatments, including chemotherapy, surgical therapies and nutritional support. Moreover, several new possible prognostic markers were shown. Here we report a summary of novel findings taken from some molecular biology sessions, focused on prognosis and treatment of GC.

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INTRODUCTION

Gastric cancer (GC) represents one of the most frequent cause of cancer death[1,2], although most of the mechanisms leading to its development have been clarified. *Helicobacter pylori* (*H. pylori*) infection, salted/smoked food consumption and E-cadherin mutations[2-4] are the main causes of stomach tumor, according to multifactoriality characterizing almost all neoplasms. Improving early diagnosis is one of the most yearned target, because of possible misunderstanding of first GC symptom. Therapies are based above all on surgery and, however, the use of drugs was recently supported by GC gene expression analysis, which led to performing target specific treatments[5,6]. Reflecting the need of a multidisciplinary approach, the (10th IGCC) predisposed several sessions in which the authors were allowed to present their results in a well targeted context. Discussed topics ranged from surgical techniques, to patient nutrition, to diagnosis and chemotherapy. We focused our attention on subjects related to possible diagnostic/prognostic factors and to molecular targeted therapies. As we report, together with novel findings about well characterized molecules, a role in GC development of markers involved in other neoplasms growth was also found. Moreover, discussed therapies provided interesting starting points, as the results obtained with natural extracts of *Capraria biflora* on a GC cell line and the treatment of a mouse model of peritoneal metastases with maraviroc, an Food and Drug Administration (FDA) approved drug used for human immunodeficiency virus (HIV) patients. Hence we can assert that the 10th IGCC gave an all-round view about GC, showing the most important trend in this neoplasm management.

NOVEL FINDINGS ABOUT E-CADHERIN

Many studies about E-cadherin (also known as CDH1) have been performed over the past several years. Its role in GC development is ascertained by now[7-9] and several germline mutations were effectively well characterized[7]. Yet, Sugimoto *et al*[10] reported the first case of a *de novo* large genomic deletion of *CDH1* associated with early-onset diffuse GC. The patient, with a deletion of the exon 11, was a 41-year-old man with no familial history of GC. His son was a carrier of the same deletion, hence according to authors' conclusions, CDH1 mutational status should be considered also in the absence of familial history of GC. Again, the investigation of CDH1 mutational status led also to decision of profilactic gastrectomy, as shown by Biffi *et al*[11]. Authors presented a case of 41-year-old female patient positive for germline CDH1 mutation, who had previously undergone surgical resection of a lobular breast cancer. The case reported by authors was the first Italian prophylactic surgical intervention, whereas in the United States this kind of radical management in carriers is usually performed[12-15].

MARKERS KNOWN IN OTHER CANCERS: POSSIBLE ROLE IN GC DIAGNOSIS AND PROGNOSIS

Nearby novel discoveries related to well-known markers, such as CDH1, novel potential diagnostic and prognostic tools were described.

Santos-Sousa *et al*[16] presented an emerging role for mesothelin, a glycosylphosphatidylinositol-anchored cell surface protein overexpressed both in mesothelioma[17-19] and in ovarian cancer[18-20]. They found that mesothelin expression in GC tissue specimens was correlated with tumor location, macroscopic appearance, Lauren histological classification and stage. Moreover, its cytoplasmic expression was correlated with lymphatic invasion and associated with poorer survival. In 2012, Baba *et al*[21] discussed the role of mesothelin in GC development and its possible usefulness as a prognostic factor. They found that patients positive for mesothelin expression in gastric tissues showed broader nodal involvement and deeper tumor invasion. Yet, when the analysis was limited to only advanced GC cases, a higher survival rate was found in mesothelin positive patients. Considering the papers of Santos-Sousa *et al*[16] and of Baba *et al*[21], it can be inferred that mesothelin is an independent prognostic factor of GC, as stressed from authors themselves. But the first authors showed its cytoplasmic placement as a key element in exerting prognostic role, whereas the second ones referred its expected cell membrane localization. Hence further studies are necessary to better answer questions about mesothelin expression and localization so as to improve our knowledge on its role in GC development.

Few contributions were presented about the role of cell cycle regulators in stomach tumor development. Very interesting were the results presented by Kim *et al*[22], which focused their attention on p16 protein, whose expression was found lost in other neoplasms[23-26]. The same result was obtained in intestinal histotype of GC from the analysis performed by the authors, who showed that loss of p16 expression was related to a higher rate of cancer recurrence and poorer 5-year disease-free survival. This finding led the authors to hypothesize a role of loss of p16 expression in GC development, which is similar to data observed in other cancers.

Stomatin-like protein 2 (SLP-2) is a protein belonging to the stomatin superfamily, which has been found overexpressed in several kind of tumors[27]. Its overexpression is generally associated with poor prognosis in esophageal squamous cell carcinoma, human gallbladder cancer and HER2 negative breast cancer[27-29]. Liu *et al*[30] confirmed SLP-2 as a prognostic tool to manage GC. High level of SLP-2 expression was significantly associated with the depth of invasion, lymph node and distant metastases, and tumor node metastasis (TNM) stage in

GC. Notch1 is another possible marker overexpressed in GC, as shown in two independent cohort studies performed by Chu *et al*[31]. Both of them showed that higher Notch1 expression was correlated with a shorter survival time, while lower Notch-1 expression was correlated with a better survival of GC patients. These results suggest that Notch1, whose prognostic role was found in other tumors[32,33], has a predictive role in clinical outcomes of GC patients too. Moreover, the authors highlighted the dependence of Notch1 prognostic value on p65 status, hypothesizing a role as a promising novel target for GC therapy.

An unexpected result was reported by Chen *et al*[34]. They found that CD44 positive expression in surgical specimens of primary GC was not correlated with clinicopathological features and survival outcomes. These data may be considered surprising because CD44 is a well-recognized tumor marker[35-37]. It may be possible that GC development is independent from CD44 expression levels, although it has to be mentioned that in 2013, a paper of Hirata *et al*[38] was published, in which the authors found a correlation between expression of a CD44 variant and GC recurrence.

Epigenetic control of DNA expression was often found pivotal in etiogenesis of various cancers, since it leads to gene silencing and therefore to loss of expression of oncosuppressors too[39-41]. Calcagno *et al*[42] investigated the expression levels of enzymes with methyltransferase activity, showing that they may exert an important role in GC development. They found high levels of DNMT1, DNMT3A and DNMT3B (DNA-methyl-transferase 1, 3A and 3B) expression in gastric adenocarcinoma tissues, when compared to normal specimens. However, they found no correlation between DNMT1, DNMT3A and DNMT3B overexpression and clinicopathological features, drawing the conclusion that the increased expression may be placed in the early stage GC development. Besides, the same authors investigated the effects of hypermethylation in GC cell lines[43]. They treated two gastric adenocarcinoma cell lines, ACP02 (diffuse-type) and ACP03 (intestinal-type), with a demethylating agent and evaluated gene expression compared to untreated cells. The genes neuritin 1 (NRN1) and tumor necrosis factor alpha-induced protein (TNFAIP) were found upregulated in both GC cell lines compared to controls, while metastasis associated lung adenocarcinoma transcript 1 (MALAT1) and small nucleolar RNA D (SNORD) were overexpressed only in intestinal-type GC cell line. They obtained these data as before by microarray assay and confirmed them by real-time PCR, finding new genes epigenetically altered in GC. Also, the overexpression of nonmuscle myosin IIA (NMIIA) may be associated with progression and poor prognosis of GC, as revealed by Liu *et al*[44], because high expression of this protein is significantly correlated with the depth of wall invasion, lymph node metastasis, distant metastasis and TNM stage. Another very interesting prognostic tool was presented by Choi[45], who found that in GC patients, the number of loss of eterozygosity (LOH) may be a determinant poor prognostic factor. The author analyzed LOH of 5 chromosomes having tumor suppressor genes such as p16, PTEN, Rb, E-cadherin and p53 in 100 surgically resected tumors. Patients with 2 or more LOHs displayed a poorer 5-year survival rate than those who had less than 2 LOHs. In particular, LOH in 17p13 (p53 locus) contributed to a lower survival rate. Therefore, the number and the type of LOH in GC may be useful prognostic indicators. A very innovative diagnostic tool was presented by Linē *et al*[46], who identified a tumor-associated autoantibody signature that can be used for the early detection of GC among high-risk individuals. The autoantibody production, which does not correlate with histotype, already occurs in early GC and it could be associated with shorter overall survival. *H. pylori* status, grade, localization and size of the primary tumor were not related to autoantibody signature. Diagnosis of GC at advanced stages is considered a major reason for lower five-year overall survival rate in developing countries[47]. Hence, early diagnosis of GC is fundamental for patient survival.

VASCULAR ENDOTHELIAL GROWTH FACTOR AS POSSIBLE GC MARKERS

VEGF (vascular endothelial growth factor) has been largely investigated because of its active role in angiogenesis. It was found that its overexpression is a poorer prognostic marker in various neoplasms such as osteosarcoma[48], non-small cell lung carcinoma[49] and melanoma[50].

Some authors analyzed the expression levels of VEGFs either alone, or together with other possible prognostic factors. Kruszyna *et al*[51] showed that VEGF, hypoxia inducible factor-1 (HIF-1) and CXC chemokine receptor 4 (CXCR4) were up-regulated in tumoral, but not in normal specimens. Von Hippel-Lindau tumor suppressor (VHL) and HIF-prolyl hydroxylase 2 (PHD2) were, instead, expressed at very low levels in tumor tissues. All these results were found related with malignant tumor progression and lymph node metastasis, drawing attention to the possibility of considering VEGF, CXCR4, VHL and PHD2 as prognostic markers of GC. Noteworthy were also the results obtained by Partika *et al*[52]. Although in few patients, they observed the absence of VEGF within the GC tissue despite its high plasma concentration. The authors hypothesized that VEGF in somehow was quickly eliminated into the blood stream. Hence, further investigations may be useful to cast light on the possibility to use plasma levels of VEGF as a biomarker. Finally, Yingwei *et al*[53] investigated the expression levels of VEGF, EGF and their receptors in GC cell lines of different biological properties and the outcomes of their targeted inhibition. They found that EGF, EGFR, VEGF and VEGFR mRNA expression increased sequentially in SGC7901, BGC823, HGC27 and MGC803 cell lines, allowing them to increase their proliferation, motility and adhesion. Therefore, spe-

cific inhibition of VEGF and EGF may impair cellular properties related to tumoral phenotype, representing a possible therapeutic strategy for GC. On the other hand, Donizy *et al*[54] have not found any clinical significance of VEGF-C, VEGF-D, VEGFR-3 expression in GC patients. The only statistically significant parameter which they found related to poor prognosis and shorter long-term survival was the lower level of matrix metalloproteinase-2 (MMP-2). Hence it can be deduced that, although there are some exceptions, VEGF pathways may be considered as possible prognostic tools and/or therapeutic targets.

MICROSATELLITES INSTABILITY

Interesting studies about prognostic significance of microsatellites instability (MSI) were also presented. Pascale *et al*[55] analyzed the differences in MSI between two groups of patients living in higher and lower Italian risk areas. The authors found that GC patients living in higher risk areas showed a higher rate of MSI than those in low-risk areas. These results stress the relationship among environment, genome and cancer, topic of investigations for a long time. Although not always demonstrated, it is undeniable that many authors contributed to reinforce the aforementioned relationship. The analysis performed by Pascale *et al*[55] is hence particularly interesting because it highlighted the clinical implications derived from possible impact of environment on human genome. Kim *et al*[56] presented similarly interesting results, related to role of MSI in GC medical evaluation. They studied the link between the MSI-high (MSI-H) and GC prognosis in patients who underwent gastrectomy. In few patients MSI-H was detected and there was no relationship with lymph node involvement. Yet, MSI-H correlated with a poorer prognosis than MSI-low (MSI-L) and microsatellite stable (MSS) context. It has to be noticed that in literature different results were reported too. Some authors showed that MSI-H was related to a better prognosis[57-59], whereas others reported no significant correlation between MSI and GC prognosis[60,61]. And in more recent reviews, the role exerted by MSI in GC development is discussed but not definitely clarified[62]. Hence it can be deduced that far from being well understood, the role of MSI in GC, although challenging cues were provided during the 10th IGCC, deserves further investigations in order to better clarify its role in GC development.

TREATMENT AND THERAPY OF GC

One of the most challenging topics of the 10th IGCC, representing also one of the most innovative section of 10th IGCC, was referred to biomolecular analysis of therapeutic management of GC. Various authors obtained promising results, identifying novel potential therapeutic tools that could have a future clinical application. Liu *et al*[63] identified a novel immunological method that can not only detect GC cells and but also inhibit migration and invasion. In particular, a functional monoclonal antibody (mAb) MS57-2.1 against novel antigenic markers on the gastric cancer cell surface, MS57A and MS57B, was generated. Both antigens are membrane bound glycosylated enzymes and belong to the alkaline phosphatase family[64]. MS57-2.1 mAb was produced by hybridoma method and it was able to bind specifically to GC cell membrane with high affinity. Through this binding, a cellular signal inhibiting tumor cell migration and invasion was found activated *in vitro* and tumor metastasis impairment was detected *in vivo*. Hence, MS57-2.1 mAb could represent an effective novel tool in GC therapy because it may help to impair progression of tumoral phenotype. Other authors tested the effect of drugs both *in vitro* and *in vivo* experiments. *In vitro*, Calcagno *et al*[65] evaluated the cytotoxic and genotoxic potential of E-2-Benzo[D]thiazol in normal and gastric tumor cells (ACP02 - diffuse-type gastric adenocarcinoma cell line). Their results showed DNA damage and apoptosis in tumor cells, without significant damage to lymphocytes. These findings suggest E-2-Benzo[D]thiazol as a potential drug to improve GC management. Protein kinase D (PKD) inhibitor CID755673 may be another anti-neoplastic treatment for GC, as shown by Tsuboi *et al*[66]. PKD regulates multiple normal and abnormal biological processes, including angiogenesis[67,68]. VEGF pathway seems to be an important driver of tumorigenesis in GC, as previously reported[69,70], also in a paragraph above. Analysis of mechanism of action of CID755673, performed in MKN45 cell line, showed inhibition of PKD phosphorylation, induced by phorbol myristate acetate, and of VEGF secretion levels in a dose-dependent manner. Hence, PKD inhibitors may contribute to angiogenesis regression in GC. In an *in vivo* model, Graziosi *et al*[71] studied the effect of maraviroc, a chemokine CCR5-receptor antagonist, in GC treatment. Maraviroc is the first member of a new class of antiretroviral drugs, whose mechanism of action is pivoted on blocking R5-tropic HIV entry into CD4 cells[72,73]. It was approved by United States FDA to be used, in combination with other antiretroviral agents, for treatment of patients carrying both drug-sensitive and -resistant HIV strains[74]. In cancer, metastasis prevention induced by maraviroc was observed in hepatocellular carcinoma[75] and basal breast cancer[76,77]. In their study, Graziosi *et al*[71] analyzed a mouse model of peritoneal carcinomatosis in which maraviroc reduced both GC cell dissemination and tumor growth. These findings provide evidences for an important role of CCR5 in cancer cell invasiveness, suggesting also a possible use of maraviroc as a further therapy to reduce the risk of metastasis in GC patients. Finally, among the various possible chemotherapeutic strategies, it has to be mentioned the potential efficacy of biflorin, a prenyl-ortonaftoquinone obtained from the roots of Capraria biflora L., in ACP02 cell line. Calcagno *et al*[78] reported that biflorin exerts anticancer activity; it inhibits both tumor cell line growth in culture and tumor development in mice[79,80]. In fact, biflorin showed a powerful cytotoxic effect *in vitro*, inhibiting cell

proliferation, migration and invasion. Moreover, after treatment, morphological analysis spotlighted cell death by necrosis. Results obtained by authors seemed to be focused on a possible reduction of MYC copy number in ACP02 and in the length of telomeres, to give a possible explanation for biflorin effects.

CONCLUSION

The 10th IGCC gave a complete overview about the state-of-the-art of stomach tumor management. Both in the basic research and in clinical activity, there has been a great knowledge improvement. In our opinion, original suggestions were particularly found in therapy and treatment sections. Treatment of GC with Maraviroc, generally used in HIV patients, may be a turning point, so as the promising possible use of biflorin. Yet, due to complexity of GC etiogenesis, further studies will be necessary and will have to be performed for a long period of time to reach the target of a gold standard therapy.

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