SPANDIDOS PUBLICATIONS

ONCOLOGY LETTERS 11: 2959-2964, 2016

Lauren classification and individualized chemotherapy in gastric cancer (Review)

JUNLI MA[1,2], HONG SHEN[2,3], LINDA KAPESA[1] and SHAN ZENG[1,2]

[1]Department of Oncology; [2]Key Laboratory for Molecular Radiation Oncology; [3]Institute of Medical Sciences, Xiangya Hospital, Central South University, Changsha, Hunan 410008, P.R. China

Received January 10, 2015; Accepted February 5, 2016

DOI: 10.3892/ol.2016.4337

Abstract. Gastric cancer is one of the most common malignancies worldwide. During the last 50 years, the histological classification of gastric carcinoma has been largely based on Lauren's criteria, in which gastric cancer is classified into two major histological subtypes, namely intestinal type and diffuse type adenocarcinoma. This classification was introduced in 1965, and remains currently widely accepted and employed, since it constitutes a simple and robust classification approach. The two histological subtypes of gastric cancer proposed by the Lauren classification exhibit a number of distinct clinical and molecular characteristics, including histogenesis, cell differentiation, epidemiology, etiology, carcinogenesis, biological behaviors and prognosis. Gastric cancer exhibits varied sensitivity to chemotherapy drugs and significant heterogeneity; therefore, the disease may be a target for individualized therapy. The Lauren classification may provide the basis for individualized treatment for advanced gastric cancer, which is increasingly gaining attention in the scientific field. However, few studies have investigated individualized treatment that is guided by pathological classification. The aim of the current review is to analyze the two major histological subtypes of gastric cancer, as proposed by the Lauren classification, and to discuss the implications of this for personalized chemotherapy.

Contents

Correspondence to: Professor Shan Zeng, Department of Oncology, Xiangya Hospital, Central South University, 87 Xiangya Road, Changsha, Hunan 410008, P.R. China
E-mail: zengshan2000@yeah.net

Key words: gastric cancer, Lauren classification, intestinal type, diffuse type, individualized chemotherapy

1. Introduction

Gastric cancer is the fourth most common type of cancer and the second leading cause of cancer-associated mortality worldwide (1). Annually ~1,000,000 individuals are diagnosed with gastric cancer worldwide, resulting in 800,000 mortalities (2). The incidence of gastric cancer predominates in populations from certain geographical locations and socio-economic groups, which is considered to mainly be associated with variations in diet (1). High-incidence areas include East Asia, Eastern Europe, Central and South America, Japan and Korea, while low-incidence rates are observed in South Asia, North and East Africa, and North America (3).

Worldwide mortality rates for gastric cancer have declined in the past 10 years, however the survival rate remains low (4). Although numerous novel chemotherapy regimens have been developed for the treatment of gastric cancer, the sensitivity to treatment differs in every patient. The histological classification, in particular Lauren classification, may aid to screen patients with specific drug sensitivities.

2. Characteristics of Lauren classification

According to Lauren's criteria, gastric cancer is classified into two main types: Intestinal and diffuse type (5). Intestinal and diffuse gastric cancer exhibit numerous differences in pathology, epidemiology and etiology (5,6).

Clinical and pathological characteristics of intestinal and diffuse gastric cancer. In intestinal tumors, tumor cells exhibit adhesion, are arranged in tubular or glandular formations and are often associated with intestinal metaplasia (5). This type of gastric cancer is associated with lymphatic or vascular invasion, and the lesions are scattered in distant positions. Intestinal gastric cancer most commonly occurs in elderly male patients, affects the gastric antrum, and exhibits a longer course and better prognosis (6,7).

By contrast, in diffuse gastric cancer, tumor cells lack adhesion and infiltrate the stroma as single cells or small subgroups, leading to a population of non-cohesive, scattered tumor cells (6). Intracellular mucus may push the nucleus of the cell aside to form signet-ring cell carcinoma. The diffuse type is associated with patients of younger age and exhibits a predilection for females compared with the intestinal type (5).

Peritoneal metastasis of diffuse gastric cancer, without easily recognized precursor lesions is common. This type of cancer usually affects the body of the stomach, and presents shorter duration and worse prognosis compared with the intestinal type (6,8).

Epidemiological characteristics of intestinal and diffuse gastric cancer. Intestinal gastric cancer is more prevalent in high-risk areas, while the diffuse type is more prevalent in low-risk areas (9). In recent years, the worldwide incidence of intestinal and diffuse gastric cancer has decreased, although the decline in the diffuse type has been more gradual compared with the intestinal type, with an evident shift in histological subtype from intestinal to diffuse type adenocarcinomas (10). The tumor location in the stomach has also changed due to an increase in the incidence of gastric cardia cancer and a decrease in distal cancers (11). This trend is particularly evident in the West.

Etiology and pathogenesis of Lauren classification. The pathogenesis of intestinal and diffuse gastric carcinoma involves DNA methylation, histone modifications and chromosome recombination (12,13). The two subtypes share common dietary and environmental risk factors, however, the intestinal type is more associated with environmental factors, whereas the diffuse type usually presents a genetic etiology (2).

Etiology of intestinal gastric cancer. Helicobacter pylori (HP) infection combined with diet and environmental factors is associated with the development of intestinal gastric cancer (2). The carcinogenic process involves multiple steps, including atrophic gastritis, intestinal metaplasia, dysplasia and ultimately gastric carcinogenesis (14).

HP is considered to be the promoter of intestinal gastric cancer, however, the hypothesis that HP eradication would prevent gastric cancer remains controversial. Previous studies (15,16) have suggested that the process preceding high-level neoplasia is potentially reversible, and that the eradication of HP may decrease the probability of gastric atrophy and intestinal metaplasia, thus leading to the prevention of gastric cancer. However, certain studies have indicated that the risk of developing gastric cancer remains even once the HP infection is cured (17,18). Furthermore, a previous meta-analysis revealed that curing HP infection may reduce the incidence of chronic atrophic gastritis, however, this may not prevent the development of intestinal metaplasia (19). HP eradication does not decrease the incidence of metachronous gastric carcinoma (20). Therefore, further prospective studies are required to investigate the role of HP eradication in the development of gastric cancer.

Etiology of diffuse gastric cancer. Diffuse gastric carcinoma originates from the gastric mucosa and is associated with gastritis (21). Thus, it is less affected by environmental factors than the intestinal type, although HP infection may be also involved in the development of diffuse gastric carcinoma (22). However, contrarily to intestinal gastric cancer, the diffuse type develops as a direct result of chronic active inflammation, bypassing the intermediate steps, which include atrophic gastritis and intestinal metaplasia (23). Active gastritis is considered to be a major risk factor for diffuse gastric cancer. A previous study reported that the level of DNA methylation in gastric mucosa is closely associated with HP-related gastritis, and that there may be a molecular mechanism underlying the development of diffuse gastric cancer (24).

Hereditary diffuse gastric cancer (HDGC). Of all gastric carcinomas, ~80-90% are sporadic, while 10% exhibit a familial cluster; and 1-3% patients with familial hereditary gastric cancer demonstrate particular genetic patterns (25). Familial gastric cancer includes HDGC, familial intestinal gastric cancer and familial diffuse gastric carcinoma (26,27). A total of 40% of HDGC cases exhibit the characteristic E-cadherin [also known as cadherin 1, type 1 (CDH1)] gene germline mutation. To date, >100 germline CDH1 alterations have been identified, which mainly include point mutations and large deletions (28).

CDH1 mutations lead to decreased expression of CDH1, which decreases cell adhesion and activates multiple signal transduction pathways, leading to tumor invasion and metastasis. The 'two-hit theory' hypothesizes that the mutation of one allele of the CDH1 gene does not affect the expression of CDH1 (29). However, inactivation of the other allele leads to the corresponding change in protein expression (29). These two 'hits' may include methylation, somatic mutations and loss of heterozygosity. In addition, missense mutations in the tumor protein p53 and c-Met genes may also be involved in the pathogenesis of HDGC (29,30).

Sporadic diffuse gastric cancer. Previous studies have demonstrated that the CDH1 mutation also occurs in sporadic diffuse gastric carcinoma (31-33). The mutation frequency is hypothesized to be <10%, however, no clear statistical data has been reported thus far (34).

Varying from the aforementioned classical two-hit model of tumor suppressor gene inactivation, CDH1 promoter methylation may function as the second hit in the early onset of diffuse type gastric cancer (29,35). As CDH1 is currently the only unequivocal gene mutated in such patients, screening for CDH1 mutations may be recommended for suspected cases of diffuse gastric carcinoma (36).

In patients with family history of diffuse gastric carcinoma, who present the aforementioned CDH1 mutation, endoscopy should be strengthened, or preventive total gastrectomy may be recommended, as CDH1 mutation carriers have a lifetime risk of 70-80% of developing diffuse gastric cancer (37,38).

3. Biomarkers of Lauren classification

Certain genes or proteins exhibit different levels of expression in intestinal gastric cancer, compared with diffuse gastric cancer (39-41). Thus, these genes may constitute biomarkers and may represent two different mechanisms of pathogenesis. However, the specific role of such biomarkers remains to be elucidated in order to predict the prognosis of gastric cancer.

CDH1. CDH1 mediates cell adhesion and maintains the integrity of cellular structures. Previous studies have reported that the expression of CDH1 is significantly higher in intestinal gastric cancer than in the diffuse type (42-44), which may be

associated with the degree of differentiation. CDH1 expression is lower in less-differentiated tissues (45). Thus, CDH1 expression appears to be an early event in gastric cancer, and may serve as a useful marker for clinical prediction of gastric carcinoma.

Caudal type homeobox-2 (CDX-2). CDX-2 is important in the development of the intestinal mucosa and in maintaining cell morphology. CDX-2 does not appear in the normal gastric mucosa, but is expressed abnormally in intestinal metaplasia and intestinal gastric cancer (46,47). The expression levels of CDX-2 are markedly higher in intestinal gastric cancer compared with the diffuse type (46,47). A previous study indicated that CDX-2 activates the expression of the mucin 2 gene in gastric cells, inducing an intestinal trans-differentiation phenotype (48). Comparison of dysplasia and CDX-2 expression in cancer tissues has revealed that CDX-2 expression is higher in intestinal metaplasia tissues compared with the diffuse type (49), indicating that CDX-2 expression may represent an early event in gastric cancer. The majority of studies consider CDX-2 to be a positive prognostic factor (50-52).

Microsatellite instability (MSI). In total, ~20% of gastric carcinomas may be characterized by MSI, which is more common in the intestinal type compared with the diffuse type of gastric cancer (40). However, MSI is a controversial prognostic factor. Previous studies have reported that tumors with MSI exhibit a better prognosis (40,53).

Other authors hypothesize that tumors with high MSI exhibit more aggressive biological behavior, leading to a poor prognosis (54). Thus, further studies on MSI, including efficacy of fluorouracil therapy, are required to guide clinical treatment.

Human epidermal growth factor receptor 2 (HER2). HER2 is a member of the HER family. Trastuzumab is used for the treatment of tumors exhibiting positive HER2 expression. Positive expression rates of HER2 in gastric cancer are reported to range from <10 to 30% (55). The expression of HER2 is associated with pathological tumor type. The majority of studies suggest that the HER2 positive rate is higher in the intestinal type of gastric carcinoma, compared with the diffuse type (56-58).

HER2 is involved in cellular differentiation, adhesion and apoptosis, thus being important in the development of several tumors (59,60). However, the prognostic value of HER2 expression in gastric cancer remains unclear. Certain studies have indicated that gastric cancer patients with positive HER2 expression exhibit a shortened overall survival and no disease-free survival period compared with patients with negative HER2 expression (56,61). However, other studies have reported that HER2 expression is not associated with disease prognosis (57,62). There is little evidence regarding whether HER2 may be used as prognostic factor according to the various pathology types of gastric cancer.

In addition, a number of molecules that are differentially expressed in various gastric cancers, including tumor-associated calcium signal transducer 2, thrombospondin 4, mothers against decapentaplegic homolog 4 and the family of transcription factors snail family zinc finger 1, have been identified (63-66). These molecules may constitute potential biomarkers of different gastric cancer subtypes. Due to the high mortality rate and low survival rate, the identification of useful biomarkers to predict prognosis and guide clinical treatment is extremely important.

4. Lauren classification and gastric cancer chemotherapy

Gastric cancer is a highly heterogeneous disease, which may exhibit a variety of biological behaviors. The results of previous studies vary between the East and West and thus, it is difficult to select the optimum treatment (67). Patients exhibit different sensitivities to chemotherapy, according to Lauren classification and thus, tailoring individualized cytotoxic therapy for the treatment of gastric cancer is becoming an area of increasing interest within the scientific field (5).

Chemotherapy-associated gastric cancer genes. Chemotherapy regimens for gastric cancer have varied considerably since the 1980s. The most common chemotherapy regimens for the treatment of gastric cancer include 5-fluorouracil (5-FU), platinum, taxane, irinotecan and anthracycline. These drugs may be administered separately, using double- or triple-drug regimens in combination with epirubicin or docetaxel.

The drug-related gene, thymidylate synthetase, is the major target of 5-FU. Excision repair cross-complementing 1 and class III β-tubulin are associated with the sensitivity of cancer cells to platinum or taxane-based chemotherapy, respectively.

Detecting expression of drug-related genes prior to treatment may contribute to the selection of efficient chemotherapy drugs and to design optimal chemotherapy regimens for gastric cancer. Predicting treatment response requires comprehensive analysis of several chemotherapy-associated genes. It is also closely associated with gene polymorphisms (68,69). Therefore, further studies are required to provide more information with regard to biomarker-guided individualized treatment of gastric cancer.

Chemotherapy drug efficacy according to Lauren classification. At present, no optimum combined chemotherapy regimens for advanced gastric cancer exist. The number of studies investigating drug selection according to different pathological types is limited, and the majority of these studies are observational studies, phase II clinical trials or retrospective analysis.

In the Japan Clinical Oncology Group (JCOG)9912 trial (70), no significant differences in median survival time were identified between the 5-FU, capecitabine (CAP) and S-1 regimens. However, subgroup analysis indicated that S-1 and CAP were more efficacious than 5-FU in the treatment of diffuse gastric cancer. The First-Line Advanced Gastric Cancer Study (FLAGS) study (71) identified no significant differences between combined treatment with cisplatin and S-1, compared with 5-FU treatment alone. However, additional experiments revealed that the average survival time of patients with diffuse gastric carcinoma is longer compared with the patients with intestinal type of gastric cancer (9.0 vs. 7.1 months). The GC0301/TOP-002 clinical trial (72) compared the treatment efficacy of combined irinotecan

and S-1 therapy with S-1 single-agent therapy for gastric cancer. The results indicated that the median survival period has reached the statistical difference only in diffuse gastric cancer. A previous phase III clinical trial (73) reported that combined therapy with irinotecan and cisplatin improved the prognosis of patients undifferentiated gastric cancer. Therefore, single-agent therapy with paclitaxel may be used in the treatment of advanced metastatic gastric cancer. Several phase II studies with small cohorts identified that diffuse gastric cancer exhibited higher effective rates compared with the intestinal type (74,75). The S-1 and Taxotere (docetaxel) therapy for Advanced gastric cancer Randomized phase III Trial (START) study (76) revealed that combined therapy with S-1 and docetaxel was superior to monotherapy with S-1 in patients with diffuse gastric cancer. These results suggest that S-1, irinotecan and docetaxel may exhibit a certain advantage in the treatment of diffuse gastric cancer.

A number of previous studies have reported that diffuse gastric cancer is associated with peritoneal transfer, which leads to malignant ascites (5). Thus, intraperitoneal injection of paclitaxel or allied system chemotherapy (intraperitoneal injection combined with intravenous chemotherapy) represents a promising treatment option (77,78). Intraperitoneal administration of the therapeutic drug, particularly for patients with peritoneal metastasis, may sustain higher intraperitoneal drug concentrations and enhance anti-tumor activity via gradual absorption through the lymphatic system. This treatment method is particularly suitable for peritoneal metastatic carcinoma. Commonly used chemotherapy regimens in Lauren classification have not been evaluated in prospective studies thus far. Further evidence-based medicine is required for individual treatment of patients under the guidance of pathological classification.

5. Perspectives

Gastric cancer exhibits varied sensitivity to chemotherapy drugs with strong heterogeneity. Therefore, this disease may be a candidate for individualized therapy. However, numerous problems associated with the use of individualized therapy for gastric cancer remain to be solved, including the selection of drugs for the treatment of different types of gastric carcinoma, which is mostly based on the results of previous retrospective and subgroup analyses, since no prospective studies have been conducted thus far. Due to a lack of specific molecular markers, the evidence for individualized therapy in gastric cancer is rare.

Therefore, various prospective clinical trials are required to provide the basis for individualized medicine. Treatment efficacy in gastric cancer depends on a variety of associated genes and gene polymorphisms (55,79). Thus, genetic testing may identify specific predictive indicators of gastric cancer. In addition, predictive models are required to investigate individualized treatment options.

Furthermore, genotyping of gastric cancer may be more specific than pathological diagnosis. Genomic variants also have therapeutic implications, indicating a promising direction. Thus, individualized treatment may represent a potential treatment method, which would lead to significant progress in the treatment of gastric cancer in the future.

Acknowledgements

The present study was supported by the National Natural Science Foundation of China (Beijing, China; grant no's. 30770971, 81172470, 81070362 and 81372629).

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