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Management of gastric cancer: The Chinese perspective

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Gastric cancer in China

Gastric cancer (GC) is a heterogeneous disease with large variations across geographical regions. Although the global incidence of GC is declining, it remains highly prevalent in Asia as compared to the West (1). China is one of the countries with the highest incidence of GC, and accounts for over 40% of all new GC cases in the world (2). GC is the third leading cause of cancer mortality in China (3).

Regional differences in patient outcomes and response to treatment in GC have also been observed. In a study comparing GC patients in the Memorial Sloan-Kettering Cancer Center in New York City (n=711) with those from Korea (n=1,646), the disease-specific survival for Korean patients was significantly better after adjusting for all known confounding factors (hazard ratio of 1.3, P=0.05) (4). Similarly in the AVAGAST trial, a phase III study of first-line chemotherapy plus bevacizumab in advanced GC, the intrinsic prognosis of Asian patients was shown to be better than Americans; however, the addition of bevacizumab to chemotherapy improved the survival of American patients only (5). Regarding safety in systemic treatment for GC, a meta-analysis of 8 Asian and 17 Western or international trials showed that geographical region (Asian *vs.* non-Asian) was an independent predictor, with Asian trials associated with lower incidence of grade 3-4 neutropenia and diarrhea (6).

There are postulations that these geographical differences in epidemiology and patient outcomes may be explained by distinct tumor biology and etiology. A number of gene polymorphisms, including those of the DNA repair gene XRCC1, were found to be associated with GC risk in the Chinese population (7-10). Other studies suggested differential prevalence of oncogene mutations in China and other parts of the world. For example, while RAS

mutations were reportedly rare in Western Europe and Japan, their prevalence in China was up to 30% (11-13). The prevalence of *PIK3CA* mutations was however much lower in a Chinese cohort than generally reported (14). Furthermore, differences in GC genetic instability patterns across geographical origins may also exist, as suggested by a study comparing African patients and those from the United Kingdom (15).

The high prevalence of *Helicobacter pylori* (*H. pylori*) infection and the local circulating genotypes being highly carcinogenic (16) are of particular etiological significance in China and contribute to the geographical difference. A randomized placebo-controlled primary prevention trial in China demonstrated a reduction in GC development with eradication of *H. pylori* in the subgroup of healthy carriers without precancerous lesions at baseline, although the overall incidence of GC in the eradication and placebo groups was similar at 7.5 years (17). The association between the decline in *H. pylori* prevalence in China and the decline in gastric cancer incidence was also reported by an epidemiological study (18).

Other environmental factors such as lifestyle, diet and socioeconomic status play a role in gastric carcinogenesis. China is the largest tobacco production and consumption country in the world, consisting of more than 300 million current smokers (19), and GC risk among the Chinese population is significantly associated with tobacco smoking as shown in a meta-analysis (20). The Chinese taste for preserved, salty, fried foods and hot soup, and the low intake of certain vitamins and micronutrients are associated with risk of GC (21). Concordantly, dietary supplementation of nutrients such as vitamin C, selenium and carotene was shown to prevent GC in Chinese (22,23) but not in Caucasian populations (24,25).

On the other hand, part of the perceived geographical difference in GC may simply be related to regional variation in the prevalence of different GC subtypes and their different prognosis. While proximal tumors are more common in industrialized nations and tumors of the intestinal histology in Asia, there is no evidence that patient outcomes for particular subtypes differ between regions (26). Different patient outcomes may also be explained by variation in population screening programs; at diagnosis tumors are generally of earlier stage in Korea than in the United States (4).

Taken together, GC in Chinese patients is different from that occurring in the West, and is a significant health burden. Moreover, there is currently no internationally accepted standard treatment regimen and clinical practice varies widely across countries. An updated guideline specific for the Chinese population is therefore warranted. The *Gastric Cancer Diagnosis and Treatment Expert Panel of the Chinese Ministry of Health: Chinese guidelines for diagnosis and treatment of gastric cancer (2011 edition)* (“the Chinese Guidelines”) are timely published in the latest issue of *Translational Gastrointestinal Cancer* (27). While the Chinese Guidelines provide a comprehensive account in the scientific area, a few points will be highlighted here.

Surgical and adjuvant treatment

Extended (D2) lymph node dissection is recommended in the Chinese Guidelines as the standard surgery for operable GC except for early disease limited to the mucosa or submucosa with no lymph node involvement. Although D2 resection is regarded as the standard of care in Asia, its role has been more controversial in the West, where previous trials failed to show any survival advantage with D2 over D1 dissection (28-31). However, more recent long-term follow-up results of a Dutch trial showed D2 surgery was associated with a lower rate of disease-related death than D1 surgery (32). Given that other reports from Western countries confirmed better outcomes with D2 surgery when performed in experienced centers (33-35), latest Western guidelines now recommend the inclusion of D2 dissection as the standard surgery for GC (36).

Adjuvant treatments currently used in the West, including peri-operative chemotherapy (37) or post-operative chemoradiation (38), were established before D2 surgery became standard. The less aggressive surgery may explain the benefits of the more intensive adjuvant treatments. On the other hand, post-operative chemotherapy alone is effective as adjuvant treatment after

D2 surgery in Asian trials (39,40). Moreover, a Korean study comparing chemotherapy with or without radiotherapy after D2 surgery did not show improved outcomes with the addition of radiotherapy (41). These findings support the choice of adjuvant therapy based on the level of surgery (D2 versus D0/1) performed, as detailed in the Chinese Guidelines.

Systemic therapy for advanced disease

Systemic options to treat advanced GC including chemotherapy and targeted therapy are similar in the East and West. In particular, the addition of trastuzumab to chemotherapy significantly improved response, progression free survival and overall survival in advanced GC patients with human epidermal growth factor (HER)-2-positive disease, defined by immunohistochemical (IHC) staining 3+ or fluorescence in-situ hybridization (FISH)-positive, in the phase III ToGA trial (42). The greatest benefit was seen in patients with higher levels of HER2 expression with either IHC3+ or IHC2+ plus FISH+. HER2-positive rate is higher in gastroesophageal junction (GEJ) than gastric cancers, and in the intestinal subtype than diffuse types (43). Although there is a lower percentage of GEJ carcinoma and a higher percentage of diffuse-type histology in Asia (6), interestingly the average HER2-positivity rate for European countries is similar to that observed in Asian countries (44). To date, trastuzumab is the first and only targeted agent in gastric cancer approved by both the United States (45) and European authorities (46). It is indicated in combination with cisplatin and capecitabine or 5-fluorouracil in the first line treatment of HER2-overexpressing advanced GC; strong HER2 expression with IHC3+ or IHC2+ plus FISH+ is required by the European and Chinese guidelines.

The development of other targeted agents in advanced GC has however made slower progress. The addition of bevacizumab to chemotherapy did not result in significant OS benefit in the phase III AVAGAST trial (5); more recently the results of the REAL-3 study in abstract form reported an inferior OS with the addition of panitumumab to chemotherapy (47). Data on other agents are still awaited. Currently, prospective biomarker-driven clinical trials dedicated to specific patient populations enriched with rational molecular targets are lacking. The population-based difference in the epidemiology and possibly biology of GC calls for international collaboration in future biomarker and clinical studies.

Alternative therapy

The Chinese Guidelines included traditional Chinese medicine (TCM) to be considered as part of supportive care for GC. TCM is a holistic system of medicine including herbal medicine, acupuncture and moxibustion, tuina, dietary therapy, and qigong (48). There has been a long history of using TCM in treating various diseases including cancer in China. It is believed that TCM may lead to potential benefits such as reducing side effects of chemotherapy and radiotherapy, improving patients' immune function, and enhancing the effects of conventional cancer treatments (49).

Despite the plethora of case reports and series on TCM in cancer care (48,50), large-scale well-designed clinical trials are lacking. Nevertheless, a recent report on 399 advanced GC patients with or without TCM treatment (51) represents the increasing effort to study TCM scientifically. Moreover, the Chinese government has approved the use of some Chinese herbal remedies in cancer treatment (49). It is therefore likely that TCM will continue to play a unique role in China.

Conclusions

The Chinese Guidelines addresses the need for population-specific recommendations on the management of GC. They help to arouse awareness of GC among the Chinese community, and to standardize clinical practices across China.

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