Perspective

Management of gastric cancer: The Chinese perspective

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Submitted Jun 18, 2012. Accepted for publication Jul 23, 2012.
DOI: 10.3978/j.issn.2224-4778.2012.07.07
Scan to your mobile device or view this article at: http://www.amepc.org/tgc/article/view/953

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 in 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 that 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 chemoirradiation (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.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

References

1. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol 2006;24:2137-50.
2. GLOBOCAN 2008: Cancer Incidence and Mortality Worldwide (Internet). International Agency for Research on Cancer, World Health Organization, 2010. Available online: http://globocan.iarc.fr/
3. Zhao G, Ford ES, Ahluwalia IB, et al. Prevalence and trends of receipt of cancer screenings among US women with diagnosed diabetes. J Gen Intern Med 2009;24:270-5.
4. Strong VE, Song KY, Park CH, et al. Comparison of gastric cancer survival following R0 resection in the United States and Korea using an internationally validated nomogram. Ann Surg 2010;251:640-6.
5. Kang Y, Ohtsu A, Van Cutsem E, et al. AVAGAST: A randomized, double-blind, placebo-controlled, phase III study of first-line capecitabine and cisplatin plus bevacizumab or placebo in patients with advanced gastric cancer (AGC). J Clin Oncol 2010;28:abstr LBA4007.
6. Hsu C, Shen YC, Cheng CC, et al. Geographic difference in safety and efficacy of systemic chemotherapy for advanced gastric or gastroesophageal carcinoma: a meta-analysis and meta-regression. Gastric Cancer 2012. [Epub ahead of print].
7. Shen H, Xu Y, Qian Y, et al. Polymorphisms of the DNA repair gene XRCC1 and risk of gastric cancer in a Chinese population. Int J Cancer 2000;88:601-6.
8. Yuan T, Deng S, Chen M, et al. Association of DNA repair gene XRCC1 and XPD polymorphisms with genetic susceptibility to gastric cancer in a Chinese population. Cancer Epidemiol 2011;35:170-4.
9. Peng S, Kuang Z, Sheng C, et al. Association of microRNA-196a-2 gene polymorphism with gastric cancer risk in a Chinese population. Dig Dis Sci 2010;55:2288-93.
10. Zhou Y, Li N, Zhuang W, et al. Vascular endothelial growth factor (VEGF) gene polymorphisms and gastric cancer risk in a Chinese Han population. Mol Carcinog 2011;50:184-8.
11. van Rees BP, Musler A, Caspers E, et al. K-ras mutations in gastric stump carcinomas and in carcinomas from the non-operated stomach. Hepatogastroenterology 1999;46:2063-8.
12. Hiyama T, Haruma K, Kitadai Y, et al. K-ras mutation in helicobacter pylori-associated chronic gastritis in patients with and without gastric cancer. Int J Cancer 2002;97:562-6.
13. Deng G, Eh Z, Xu Y, et al. Activation of oncogene c-Ha-ras in gastric cancer of Chinese patients. Semin Surg Oncol 1994;10:83-7.
14. Li VS, Wong CW, Chan TL, et al. Mutations of PIK3CA in gastric adenocarcinoma. BMC Cancer 2005;5:29.
15. Buffart TE, Louw M, van Grieken NC, et al. Gastric cancers of Western European and African patients show different patterns of genomic instability. BMC Med Genomics 2011;4:7.
16. Yamaoka Y, Kato M, Asaka M. Geographic differences in gastric cancer incidence can be explained by differences between Helicobacter pylori strains. Intern Med

2008;47:1077-83.
17. Wong BC, Lam SK, Wong WM, et al. China Gastric Cancer Study Group. Helicobacter pylori eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. JAMA 2004;291:187-94.
18. Yeh JM, Goldie SJ, Kuntz KM, et al. Effects of Helicobacter pylori infection and smoking on gastric cancer incidence in China: a population-level analysis of trends and projections. Cancer Causes Control 2009;20:2021-9.
19. Office CCTC. 2009 China Tobacco Control Report. Available online: http://www2.wpro.who.int/NR/rdonlyres/56A34566-34568E34567F-34564EC34563-BC34592-E869379AE869563/869370/862009CHINATFIREPORT.pdf
20. Liu N, Shen Y, Qin L et al. Meta-analysis of smoking and the risk of gastric cancer among the Chinese population. Clin Oncol Cancer Res 2009;6:296-302.
21. Ji BT, Chow WH, Yang G, et al. Dietary habits and stomach cancer in Shanghai, China. Int J Cancer 1998;76:659-64.
22. Yuan JM, Ross RK, Gao YT, et al. Prediagnostic levels of serum micronutrients in relation to risk of gastric cancer in Shanghai, China. Cancer Epidemiol Biomarkers Prev 2004;13:1772-80.
23. Blot WJ, Li JY, Taylor PR, et al. Nutrition intervention trials in Linxian, China: supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population. J Natl Cancer Inst 1993;85:1483-92.
24. Varis K, Taylor PR, Sipponen P, et al. Gastric cancer and premalignant lesions in atrophic gastritis: a controlled trial on the effect of supplementation with alpha-tocopherol and beta-carotene. The Helsinki Gastritis Study Group. Scand J Gastroenterol 1998;33:294-300.
25. Jacobs EJ, Connell CJ, McCullough ML, et al. Vitamin C, vitamin E, and multivitamin supplement use and stomach cancer mortality in the Cancer Prevention Study II cohort. Cancer Epidemiol Biomarkers Prev 2002;11:35-41.
26. Crew KD, Neugut AI. Epidemiology of gastric cancer. World J Gastroenterol 2006;12:354-62.
27. Gastric Cancer Diagnosis and Treatment Expert Panel of the Chinese Ministry of Health. Chinese guidelines for diagnosis and treatment of gastric cancer (2011 edition). Transl Gastrointest Cancer 2012;1:103-14.
28. Bonenkamp JJ, Hermans J, Sasako M, et al. Extended lymph-node dissection for gastric cancer. N Engl J Med 1999;340:908-14.
29. Cuschieri A, Weeden S, Fielding J, et al. Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. Surgical Co-operative Group. Br J Cancer 1999;79:1522-30.
30. Hartgrink HH, van de Velde CJ, Putter H, et al. Extended lymph node dissection for gastric cancer: who may benefit? Final results of the randomized Dutch gastric cancer group trial. J Clin Oncol 2004;22:2069-77.
31. McCulloch P, Nita ME, Kazi H, et al. Extended versus limited lymph nodes dissection technique for adenocarcinoma of the stomach. Cochrane Database Syst Rev 2004;CD001964.
32. Songun I, Putter H, Kranenbarg EM, et al. Surgical treatment of gastric cancer: 15-year follow-up results of the randomized nationwide Dutch D1D2 trial. Lancet Oncol 2010;11:439-49.
33. Degiuli M, Sasako M, Calgaro M, et al. Morbidity and mortality after D1 and D2 gastrectomy for cancer: interim analysis of the Italian Gastric Cancer Study Group (IGCSG) randomised surgical trial. Eur J Surg Oncol 2004;30:303-8.
34. Degiuli M, Sasako M, Ponti A, et al. Survival results of a multicentre phase II study to evaluate D2 gastrectomy for gastric cancer. Br J Cancer 2004;90:1727-32.
35. Sierra A, Regueira FM, Hernández-Lizoáin JL, et al. Role of the extended lymphadenectomy in gastric cancer surgery: experience in a single institution. Ann Surg Oncol 2003;10:219-26.
36. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology- Gastric Cancer. Version 2.2012. In Edition Available online: www.nccn.org
37. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355:11-20.
38. Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 2001;345:725-30.
39. Sakuramoto S, Sasako M, Yamaguchi T, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med 2007;357:1810-20.
40. Bang YJ, Kim YW, Yang HK, et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. Lancet 2012;379:315-21.
41. Lee J, Lim do H, Kim S, et al. Phase III trial comparing capecitabine plus cisplatin versus capecitabine plus cisplatin

with concurrent capecitabine radiotherapy in completely resected gastric cancer with D2 lymph node dissection: the ARTIST trial. J Clin Oncol 2012;30:268-73.
42. Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomized controlled trial. Lancet 2010;376:687-97.
43. Bang Y, Chung H, Xu J, et al. Pathological features of advanced gastric cancer (GC): Relationship to human epidermal growth factor receptor 2 (HER2) positivity in the global screening programme of the ToGA trial. J Clin Oncol 2009;27:4556.
44. Bang Y, Chung H, Sawaki A, et al. HER2-positivity rates in advanced gastric cancer (GC): Results from a large international phase III trial. J Clin Oncol 2008;26:4526.
45. Administration USFaD. In Edition. Available online: http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/103792s5250lbl.pdf
46. Agency EM. In Edition. Available online: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000278/WC500074922.pdf
47. Okines AF, Ashley SE, Cunningham D, et al. Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for advanced esophagogastric cancer: dose-finding study for the prospective multicenter, randomized, phase II/III REAL-3 trial. J Clin Oncol 2010;28:3945-50.
48. Yang G, Li X, Li X, et al. Traditional Chinese Medicine in Cancer Care: A Review of Case Series Published in the Chinese Literature. Evid Based Complement Alternat Med 2012;2012:751046.
49. Ma XJ, Lin C, Zhen W. Cancer care in China: A general review. Biomed Imaging Interv J 2008;4:e39. Available online: http://www.biij.org/2008/2003/e2039
50. Liu J, Li X, Liu J, et al. Traditional Chinese medicine in cancer care: a review of case reports published in Chinese literature. Forsch Komplementmed. 2011;18:257-63.
51. Xu Y, Zhao AG, Li ZY, et al. Survival Benefit of Traditional Chinese Herbal Medicine (a Herbal Formula for Invigorating Spleen) for Patients With Advanced Gastric Cancer. Integr Cancer Ther 2012. [Epub ahead of print].

Cite this article as: Wong HY, Yau T. Management of gastric cancer: The Chinese perspective. Transl Gastrointest Cancer 2012;1(2):181-185. DOI: 10.3978/j.issn.2224-4778.2012.07.07

