Review Article

Next stage of collaboration in East Asia gastric cancer treatment

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Abstract: East Asia is a high-risk area for gastric cancer (GC). Despite the rapid progress of immunotherapy and target therapy in recent years, the median overall survival (OS) of metastatic GC is still no more than 2 years. Researchers from East Asia are active in GC clinical and molecular investigations. The collaboration of East Asia plays a vital role to further GC development. Cooperation across East Asia used to be led by Japan and South Korea. However, with the tremendous success of Chinese native drug research and development (R&D) in recent years, the new era calls for a next stage for future collaboration. With the abundance of patient resources and supportive policies from the government, China GC researches made breakthroughs in anti-human epidermal growth factor receptor 2 (HER2) drugs development and immunotherapy etc. Native programmed death 1 (PD-1) inhibitors demonstrated favorable outcomes in first-line GC treatment, early phase clinical trials also showed promising results in novel drug development in the scope of biomarker-guided precisive medicine. However, chances and challenges are both upfront to this special region. There is a lack of standardization in diagnostic and treatment protocols across Asian countries, which adds the difficulties in regional clinical trials. Poor developing countries in southeast Asia are unable to support high quality early phase clinical trials and translational studies, resource deficiency may be another challenge.

Keywords: East Asia; gastric cancer (GC); collaboration

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East Asia has the highest incidence of gastric cancer (GC). Considering the large population base, the burden of GC is particularly heavy. According to the latest report of cancer epidemiology published from GLOBOCAN, the age-standardized incidence of GC is 45.7 per 100,000 person years (1). Despite the breakthroughs in immunotherapy and target therapy of GC in recent years, we are still upfront great obstacles to overcome treatment resistance and precisive medicine. The median overall survival (OS) of metastatic GC is still no more than 2 years.

We noticed the distinct principles and pattern of response to treatment between eastern and western world. For example, neoadjuvant chemoradiation therapy but not neoadjuvant chemotherapy is more common in United States (US) than East Asia. The criteria for neoadjuvant therapy patients also vary across countries, according to data from different clinical trials. Districts collaboration accelerate the development speed of GC by sharing clinical and translational research information. Thus, the union gathering adjacent countries matters to research progress.

The development of East Asia GC research plays a vital role to the world. From ToGA to CheckMate-649, leading principal investigators (PIs) from East Asia provided current evidence of target therapy and immunotherapy

Table 1 Key results of phase III clinical trial of first-line GC immunotherapy

Key results	CheckMate-649 (23% Asia)		CheckMate-649 China		Keynote-859 (33% Asia)	ORIENT-16		RATIONALE-305 (73.7% East Asia)
	CPS ≥5	ITT	CPS ≥5	ITT	ITT	CPS ≥5	ITT	PD-L1+
Study regimen	Nivo + CapeOX/FOLFOX		Nivo + CapeOX/FOLFOX		Pembro + CapeOX/FP	Sinti + CapeOX		Tisle + CapeOX/FP
Primary endpoints	PFS, OS (CPS ≥5)		PFS, OS (CPS ≥5)		OS	OS (CPS ≥5, ITT)		OS (TAP ≥5%, ITT)
N	955	1,581	156	208	1,579	397	650	546
OS (months)	14.4 *vs.* 11.1	13.7 *vs.* 11.6	15.5 *vs.* 9.6	14.3 *vs.* 10.3	12.9 *vs.* 11.5	18.4 *vs.* 12.9	15.2 *vs.* 12.3	17.2 *vs.* 12.6
HR	0.70	0.79	0.56	0.62	0.78	0.66	0.77	0.74
1-year OS rate (%)	57 *vs.* 46	55 *vs.* 48	61 *vs.* 41	57 *vs.* 43	52.7 *vs.* 46.7	–	–	59.8 *vs.* 56.7
2-year OS rate (%)	31 *vs.* 19	28 *vs.* 19	39 *vs.* 15	35 *vs.* 15	28.2 *vs.* 18.9	–	–	38.3 *vs.* 24.9
3-year OS rate (%)	21 *vs.* 10	17 *vs.* 10	31 *vs.* 11	26 *vs.* 9	–	–	–	–
PFS (months)	8.3 *vs.* 6.1	7.7 *vs.* 6.9	8.5 *vs.* 4.3	8.3 *vs.* 5.6	6.9 *vs.* 5.6	7.7 *vs.* 5.8	7.1 *vs.* 5.7	7.2 *vs.* 5.9
HR	0.7	0.79	0.51	0.57	0.76	0.63	0.64	0.67
ORR (%)	60 *vs.* 45	58 *vs.* 46	68 *vs.* 48	66 *vs.* 45	51.3 *vs.* 42.0	64 *vs.* 49	58 *vs.* 48	50.4 *vs.* 43.0

GC, gastric cancer; CPS, combined positive score; ITT, intention to treat; PD-L1, programmed death ligand 1; nivo, nivolumab; CapeOX, capecitabine + oxaliplatin; FOLFOX, 5-FU + oxaliplatin; 5-FU, 5-fluorouracil; pembro, pembrolizumab; FP, 5-FU + cisplatin; sinti, sintilimab; tisle, tislelizumab; PFS, progression-free survival; OS, overall survival; TAP, tumor area PD-L1 score; HR, hazard ratio; ORR, objective response rate.

to the world (2,3). However, different from the former stage where Japan and Korea researchers lead most the global phase III trials, the collaboration pattern in East Asia changed in line with the rapid progress of China. The development of native immunotherapy or antibody-drug conjugates (ADCs) drug platforms is comparable to US and Japan (4,5). Clinical and translational studies revealed the special biological behavior of Chinese GC patients (6).

For advanced GC, achievement of long-term survival of patients is still an unmet need. Hence, collaboration in drug research and development (R&D) is an urgent clinical need, especially in the scope of East Asia. Here, we hope to review the collaboration history of East Asia, and the future of the new era.

The past imbalance of East Asia GC development

Japan and South Korea engaged in the contemporary GC research earlier than China. In the past few decades, R&D of GC has been led by Japan and South Korea over a long period of time. China often played a subordinate role in the impletion of global multicenter randomized controlled trials (RCTs).

For chemotherapy, S-1 as a current standard oral fluorouracil regimen in East Asia, was generated from Japan (7,8). CLASSIC study which provided the standard adjuvant treatment in locally advanced GC was leaded by Korea (9). The huge success of the ToGA trial initiated the new era of anti-HER2 target therapy among GC patients, while China only participated in this landmark study and contributed subjects (2), the same as JACOB study in the era of target therapy (10). With the breakthrough of immunotherapy in the field of solid tumors, multiple international RCTs have been conducted to evaluate the utility of immune checkpoint inhibitors in the treatment of advanced GC. In line with the rapid progress in R&D in China, native programmed death 1 (PD-1) blockade products start to reshape the former circumstances (11).

Rapid progress in Chinese drug development

In recent years, immunotherapy and targeted therapy of GC have achieved rapid development in China (*Table 1*). The approval of PD-1 antibodies and targeted therapeutics (e.g., trastuzumab and ramucirumab) by the Food and Drug Administration (FDA) or National Medical Products

Administration (NMPA) for advanced GC, inspired the development of additional new medical products. From 2013 until now, there have been more than 8,000 clinical trials on cancer, involving 339 cases in GC (12). More and more drugs based on existing molecular targets bring new opportunities for GC therapy.

In immunotherapy, in pace with the success of CheckMate-649, which provided the current standard choice of PD-1 inhibitor plus chemotherapy in first-line treatment, ORIENT-16 and RATIONAL-305 also reported positive results of sintilimab and tislelizumab in first-line therapy, which are both native PD-1 blockades from China (11). Tislelizumab and envafolimab, another programmed death ligand 1 (PD-L1) inhibitor administrated via subcutaneous injection, were both approved by NMPA in second-line mismatch repair-deficient (dMMR)/microsatellite instability-high (MSI-H) GC treatment (13). There are still other ongoing national and global phase II or III RCTs leaded by China that may change the treatment landscape.

Except the success of immunotherapy, innovative target therapy and ADC drugs R&D also flourished. For example, RC48, domestically developed by RemeGen, is a novel recombinant human anti-HER2 ADC, which could trigger antibody-dependent cellular cytotoxicity (ADCC) on HER2-overexpressed cancer cells. This drug showed anti-tumor activity in patients with HER2 2+ and fluorescence in situ hybridization (FISH) negative advanced GC who were refractory or intolerant to at least two lines of standard chemotherapy, and it has been approved by NMPA (5). The success of RC48 may reshape the concept of HER2 positivity. KN026 a bispecific antibody targeting PD-L1 and cytotoxic T lymphocyte-associated protein 4 (CTLA-4) plus KN046 a bispecific antibody targeting extracellular domain (ECD) 2 and 4 of HER2 extra-membrane domain, showed favorable response rate in first-line HER2 positive GC without chemotherapy. Other agents targeting claudin 18.2 (CLDN18.2), fibroblast growth factor receptor (FGFR), and c-mesenchymal-epithelial transition (c-MET) also showed promising results in early phase trials.

Recently, CARsgen Therapeutics developed CT041, an anti-CLDN18.2 chimeric antigen receptor (CAR)-T cell therapy, which displayed a manageable safety profile and a response rate of 57.1% in advanced GC patients (14). New drugs for GC therapy have sprung out in recent years, as China is paying unremitting efforts to invest in innovative drugs development.

The steadily increasing number and quality of clinical trials in China could be the evidence. In 2017, the number of completed phase 1 clinical trials in China mainland ranked second place in the world, with 180 trials done per year (15). In recent years, Chinese researchers not only focused on participating global research, but also devoted themselves to design and conduct international research.

Future East Asia collaboration

Thanks to the open mind of NMPA in recent years, high-quality clinical trials are especially welcomed in China. As a broader land for clinical research and the great advantages of large population base, the data from China is important to the world. Here, we propose suggestions for future collaborations.

For phase 1 trials, we call for a spontaneous and broader opening site for East Asia countries. More attention to GC on early phase clinical trials is important. As other developing countries in East Asia have weak discourse power in international GC development, the inclusion of other East Asia countries such as Vietnam, Laos, and Myanmar, etc. in phase II or III clinical trials, is of great importance for the approval of novel agents and treatment strategies in these countries. China with great influence and resources in politics and economies has the ability and responsibility to widespread the newest GC research.

In consideration of adjacent districts and closely shared genetic features of GC patients, the establishment of collaborative group for GC consisting of Center for Drug Evaluation (CDE), leading PIs, and biopharma companies, may build a friendly environment for drug R&D. By sharing the data on epidemiological, prevalence and treatment outcomes of East Asian countries could help improve the patients care and regional database. Exchange programs that provide expertise and training opportunities could help build capacities and communications among foreign experts.

Challenges in East Asia collaborations

Although GC showed high incidence in East Asia, the heterogeneity in OS data may add the difficulty to study design. Japan reported discordance of survival data to China and other countries, which were hard to repeat. ATTRACTION-4, which launched mostly in Japan reported more than 20 months median OS. While in CheckMate-649, the median progression-free survival (PFS) in the nivolumab plus chemotherapy arm, the final median OS was no more than 15 months. In ATTRACTION-4,

we did not see the statistical significance, the long OS in the placebo arm may shadow the difference. Also, in DESTINY-gastric-01 study, trastuzumab deruxtecan showed long survival prolongation in third line and later line patients, however, in DESTINY-gastric-02, trastuzumab deruxtecan showed 41.8% response rate and the median PFS was 5.6 months in second-line treatment (16). The different outcomes may be due to level of support care delicate stratification of GC patients.

There is a lack of standardization in diagnostic and treatment protocols for GC across the East Asian regions, leading to variations in healthcare and outcomes. The approach to peritoneal cytology positivity or bulky lymph node is still on debate and distinct among different countries, adds the difficulty to study design.

Also, East Asian comprises of diverse populations with varying socio-economic backgrounds, health behaviors, and genetic predispositions towards GC. This can make it challenging to develop a cohesive approach towards preventing and treating the disease. Many countries in the region have limited resources for healthcare, making it difficult to invest in R&D, screening programs, and access to treatments.

Districts collaboration accelerates the development of GC. The model of East Asia cooperation may be reshaped by the rapid progress of China in recent years. The involvement in broader East Asia countries for clinical trials and close communication among the adjacent countries should be encouraged. Discordance in clinical response and principle in GC treatment adds the difficulties in study design. The next stage of East Asia collaboration is filled with chances and challenges.

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