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Minireview

Regional Differences in Advanced Gastric Cancer

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Abstract

Gastric cancer is the third leading cause of cancer-related deaths worldwide. Its prognosis is insufficient, thus warranting more effective agents in clinical applications. The efforts of several previously conducted international studies have acquired numerous anti-cancer drugs, such as trastuzumab, ramcirumab and nivolumab. However, some of the promising drugs did not show the expected endpoint. Clinical trials for these drugs were challenged by regional differences in outcomes. As overall survival is generally pre-set with regard to the primary endpoint in several clinical studies, the effect of drugs to gastric cancer significantly varies between the Asian and Western populations. This difference may be attributed to several factors, such as differences in the region, race, treatment practice and tumour burden. Thus, the minimal spread of peritoneal diseases and widespread use of second-line chemotherapy may be important factors contributing to improved overall survival in Asian patients.

Introduction

Gastric cancer is the fourth most frequently diagnosed cancer and the third leading cause of cancer-related deaths worldwide. Of approximately 1 million cases, 700,000 deaths are annually attributed to this disease [1]. More than 50% patients with gastric cancer are diagnosed at the advanced stage. Despite performing curative surgical resection, local recurrence or distant metastases are frequently encountered in clinical practice. Systemic chemotherapy is the most effective treatment of care in advanced settings. Patients treated with chemotherapy have a longer survival than those provided with best supportive care, with an approximately 6-month increase in the median survival according to a meta-analysis [2]. Thus, the development of new agents is essential to fulfil the need for extended survival, and an effective clinical trial is extremely important to acquire more effective agents. In clinical trials, particularly in international studies, result interpretation is challenged by factors such as regional differences. Overall survival (OS) rates for gastric cancer differ between the Asian and Western populations; this difference may be attributed to several factors, including differences in race, treatment practice, tumour burden, tumour biology and stage migration. Here, we have attempted to discuss the regional differences pertaining to the first three of these issues between the West and East, particularly in Japan.

Ethnic Differences

Combination chemotherapy with 5-fluopyrimidine (5-FU) and a platinum agent is commonly used to treat gastric cancer. In the USA, Japan and some parts of Europe, docetaxel is occasionally added for patients with a good general status. 5-FU is preferred in the use of S1 in Asia, whereas capecitabine is preferred in the West. The toxicities of S1 are reportedly more severe and are likely less efficient in Caucasians than in Asians [3]. Differences in the tolerability of S1 are believed to be reflective of differences in CYP2A6 gene polymorphisms between Asians and Caucasians, which affect tegafur as a prodrug of 5-FU included in S1 to 5-FU conversion. Compared with Asians, this enzyme is assumedly more powerful in Caucasians, in whom tegafur is converted to 5-FU at a greater rate to achieve a higher AUC of 5-FU at much lower doses of S1 [3]. This pharmacogenomic difference may be the reason why a lower dose of S1 was used in the FLAG study as compared with Japanese studies (SPRIT,

[4] JCOG9912, [5]). The body surface of patients in the West is generally greater than that of Japanese patients; the resultant lower dose may lead to a comparatively lower efficacy.

Regional differences in tolerability to 5-FU have been well-documented and reported. For example, in colon cancer, more gastrointestinal toxicities and neutropenia associated with 5-FU have been reported in patients from the USA than from elsewhere [6]. These regional disparities may be attributed to differences in dietary folate intake [7]. Metabolites from 5-FU are stable in the presence of reduced folate and are sustained for longer in the body. Consequently, their exposure potentially increases the type and strength of toxicities. However, these differences could not be avoided owing to differences in polymorphism patterns based on race.

Second-line Therapy

Recently, new attractive data on drugs have been revealed for gastric cancer treatment: cytotoxic, molecularly targeted and other biological agents. The results of multicentre phase 3 studies that assessed the role of second-line chemotherapy in patients with gastric cancer have been reported [8-12].

However, which regimen should be adopted as the standard of care in the second-line setting is still unestablished. For patients in whom 5-FU and platinum therapy failed, paclitaxel [11,13], docetaxel [9, 10] and irinotecan [9,13] were extensively evaluated in clinical trials. Combination chemotherapy may achieve higher response rates than monotherapy; however, their survival outcomes are similar [14]. Furthermore, compared with best supportive care alone, second-line chemotherapy significantly improved the OS in patients with advanced gastric cancer [15].

Clinical practice for second-line therapy differs from region to region. Compared with patients in other regions, a higher proportion of patients with gastric cancer in Japan receives second-line. Data from a European and Asian clinical practice reported that <50% and 67%, respectively, of their metastatic gastric cancer patients were candidates for second-line treatment [16,17]. In the SPIRIT, FLAG and REAL-2 studies conducted in Japan, >70%, 31% and 15% patients, respectively, received second-line treatment [4,5,18,19]. AVGAST, a first-line study, was a phase 3 trial of capecitabine/5-FU and cisplatin with or without bevacizumab for first-line advanced gastric cancer. The trial did not meet its primary endpoint of improving the OS as compared with that by chemotherapy alone; however, the addition of bevacizumab significantly improved the response rate (37% vs. 46%, $p = 0.03$) and median progression-free survival (PFS; 5.3 vs. 6.7 months, $p = 0.004$; [20, 21]. However, OS was the greatest benefit for patients in Pan-America, but not in Asia. We reported an exploratory analysis for regional differences in this study [22]. Here, we reported that second-line chemotherapy after disease progression was subsequently provided to 14% individuals from Eastern Europe/South America, 37% from the USA/Western Europe, 61% from Asia (excluding Japan) and 77% from Japan. The median duration of OS was 7.3 months (90% CI, 6.4–8.7) in Eastern Europe/South America, 9.1 (90% CI, 6.9–14.4) in the USA/Western Europe, 11.6 (90% CI, 79.1–15.6) in Asia (excluding Japan) and 14.1 (90% CI, 10.9–17.6) in Japan. The inverse relationship between the use of post-progression chemotherapy and OS suggests that it likely contributes to the different survival outcomes among the different regions. Thus, we speculated that the more frequent use of second-line chemotherapy in Japan contributed to the regional differences in the OS reported in the AVAGAST study.

The regional differences in the prognosis of patients in the placebo arm were also observed in the RAINBOW study—a double-blind, phase 3, randomised trial—which indicated that addition of ramucirumab to paclitaxel would offer significant survival advantages compared with paclitaxel monotherapy. Asian patients have better PFS and OS than non-Asian patients [11]. Second-line treatment may contribute to the regional differences between the West and East.

Tumour Burden

We occasionally encounter patients who are referred from surgical departments for palliative chemotherapy but have no metastatic findings on computed tomography. This patient population is considered to have good prognosis owing to the very small tumour burden as compared with that in patients with peritoneal metastasis diagnosed using less sensitive standard imaging techniques (i.e. CT or barium enema) [23]. Identification of minimal peritoneal disease has been associated with good outcomes in patients with gastric cancer [24]. To identify the relationship between prognosis and minimal peritoneal metastasis, we compared the PFS of the placebo arm in patients from Japan and the rest of world in the AVAGAST study [25]. Because the relevant diagnostic information was not recorded in this case, we could not identify the patients with minimal peritoneal metastasis diagnosed via laparoscopy or open surgery. We selected patients with minimal peritoneal metastasis as well as only peritoneal disease and no other metastases diagnosed via imaging techniques. Despite this broader definition, we attempted to elucidate the influence of OS elongation in the AVAGAST study and performed an additional exploratory analysis. For this, we enrolled 188 patients from 14 Japanese sites; of the 188 patients, 94 patients were randomised to the placebo arm. Compared with 293 patients from the rest of world in placebo arm, PFS tend to be favourable in Japan (Table 1). The Japanese patients

Table 1. PFS according to the patient subgroup.

Median PFS (months)				
Patient subgroup			**HR**	**95% CI**
	JPN [n]	**ROW [n]**		
All	5.7 [94]	4.8 [293]	1.25	0.97–1.60
Without liver mets	5.9 [71]	5.2 [189]	1.39	1.03–1.87
With PM	5.7 [52]	4.3 [120]	1.72	1.21–2.44
With only PM	8.6 [16]	5.0 [23]	2.22	1.06–4.66
Excluding only PM subset	5.5 [78]	4.7 [270]	1.11	0.85–1.46

JPN: Japan; ROW: rest of world; HR: hazard ratio; CI: confidential interval; mets: metastasi(e)s; PM: peritoneal metastasis

were categorised as those without liver metastases, with peritoneal metastasis and with only peritoneal metastasis; these patients were clearly more favourable than those from the rest of the world. The difference in the subgroup with peritoneal metastasis was particularly large with a lower confidence limit of 1.21. After excluding patients with minimal peritoneal disease from the analysis, the Kaplan–Meier PFS curve of the Japanese patients was similar to that of the patients from the rest of the world. This finding indicates that patients with peritoneal metastasis had a profound influence on the Japanese findings. Frequent radiological screening programmes in Japan have increased the detection of earlier-stage diseases, and Japanese patients are typically diagnosed before the burden of disease becomes excessive.

Consequently, the results of the AVAGAST study may have been subject to lead-time bias. This hypothesis is supported by the results of our analysis of outcomes in patients with markers of high disease burden. Regardless of the parameters used to define substantial tumour burden, patients from Japan and the rest of the world appeared to perform similarly. In contrast, among patients with a lower disease burden, the outcomes were more favourable for patients from Japan than from the rest of the world. These findings corroborated with those from other studies, which identified that low tumour burden was correlated with a positive prognostic value [26-29].

Conclusion

Racial differences, second-line chemotherapy and lesser tumour burden at the time of diagnosis, including minimal peritoneal disease and the widespread use of second-line chemotherapy, were identified as the possible important contributing factors affecting improved OS in Asian patients, particularly in Japanese patients. Although the difference in tumour burden is anecdotal due to post-hoc analysis, it may contribute to regional differences as well as to differences caused by race and preferred second-line chemotherapy. Considering the cause of regional differences while developing new chemotherapeutic agents may help provide harmonious data for application in clinical trials across the world, without the risk of regional differences.

Competing interests

The authors declare no conflict of interest.

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