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REVIEW
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Present status and perspective of chemotherapy for patients with unresectable advanced or metastatic gastric cancer in Japan

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Abstract: Patients with unresectable advanced or recurrent gastric cancer have a poor prognosis with overall survival times increasing by only a few months after anti-cancer drug therapy in the last four decades. The survival times from previous clinical trials for untreated metastatic gastric cancer in Japan are generally better than those reported from trials in European and North or South American countries. Therefore, the proportion of Japanese patients enrolled in recent global trials of novel anti-cancer drugs should be increased in order to identify drugs that specifically prolong the survival of such patients. S-1 plus oxaliplatin (SOX) therapy is the most commonly used standard first-line treatment for advanced gastric cancer in Japan. SOX induces mild nausea and vomiting, even in elderly patients, that can be treated by maintaining oral intake with adequate anti-emetic treatment usually given in an outpatient clinic. Neutropenia, nausea, and vomiting in SOX therapy were more frequently observed in female patients compared with males. Intensive toxic chemotherapy such as triplet therapy never prolonged overall survival or maintained a favorable quality of life. The current strategies used against metastatic gastric cancer need to be modified in regard to innovative treatments with current drugs, keeping in mind each categorized treatment population. In a real world of a diverse society even if the same treatment is performed, the outcome of the individual patient is different. It is important for each society to implement established treatment, knowing that the evidence from global trials aimed at drug approval does not necessarily show external validity.

***Keywords*:** gastric cancer, capecitabine, S-1, oxaliplatin, sex difference, ERCC1

Introduction

Gastric cancer is the third leading cause of cancer-related deaths worldwide. In 2018, one million new cases of gastric cancer were diagnosed and 0.8 million cancer-related deaths occurred worldwide; of these, three quarters occurred in Asia, especially in East Asia (*1*).

The prevalence and mortality rate for gastric cancer has previously been high in Japan, and the age-adjusted mortality rate has decreased significantly in the last four decades, similar to what has been observed in the United States and Western European countries since 1940 (*2,3*) (Figure 1 and Figure 2). The cause of this drop in incidence is thought to be an increase in fresh food intake, such as raw vegetables and fruits, due to the increased storage of food products because of refrigeration, a decrease in salty food intake, and a decrease in *Helicobacter pylori* infection (*4*).

Since gastric cancer, in its early stages, is often asymptomatic, it is frequently diagnosed at an advanced stage in the absence of mass screening or the active surveillance of a population. In 1995-2000, 53% of Japanese gastric cancers were localized when diagnosed, which is comparatively high against the 27% reported by the US Surveillance, Epidemiology, and End Results program (*4*).

The age-adjusted survival rates of gastric cancer between 2005 and 2009 were higher in Japan (54%) and South Korea (58%) than in Western countries (18-31%) (*5*). The survival rate for this disease has increased along with the number of trained doctors who can perform gastroscopies, allowing convenient access to clinics and hospitals for many people; however, an increase in the number of cases detected by mass screening has not occurred (*6*). The proportions of patients with pathological stage (Japanese Gastric Cancer Association) IA, IB, II, IIIA, IIIB, and IV disease between 2001 and 2007 in Japan were 44.0%, 14.7%, 11.7%, 9.5%, 5.0%, and 12.4% respectively. The 5-year overall survival rates of patients with pathological stage IA, IB, II, IIIA, IIIB, and IV disease were 91.5%, 83.6%, 70.6%, 53.6%, 34.8%, and 16.4%. The 5-year survival rate was 42% and the proportion of pT1 was 22% between 1963 and 1969.

The number of patients with early gastric cancer has increased, however, the total number of deaths due to gastric cancer in Japan has not decreased because of the increase of the elderly population (Figure 3) (*7,8*). It is also important for progress in quality of medicine

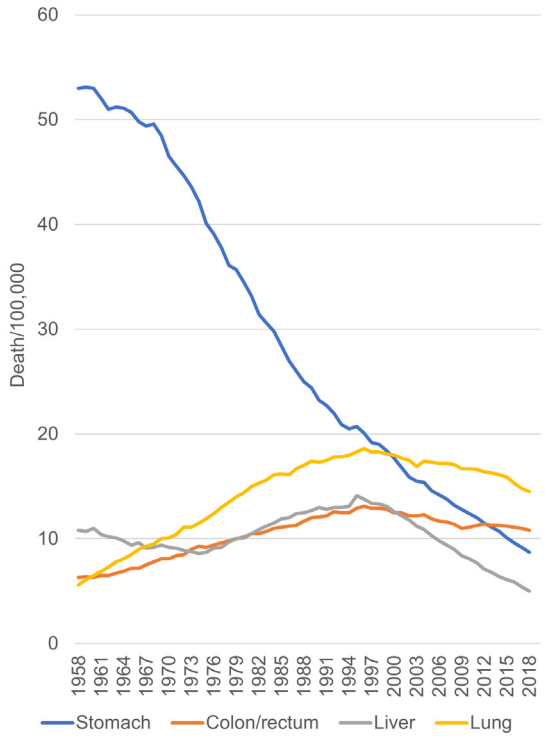

Figure 1. Trends in age-adjusted mortality rate of cancer of stomach, colorectum, liver, and lung in Japan, 1958-2018 (*3*). Gastric cancer showed a clear continuous decrease from 1960s.

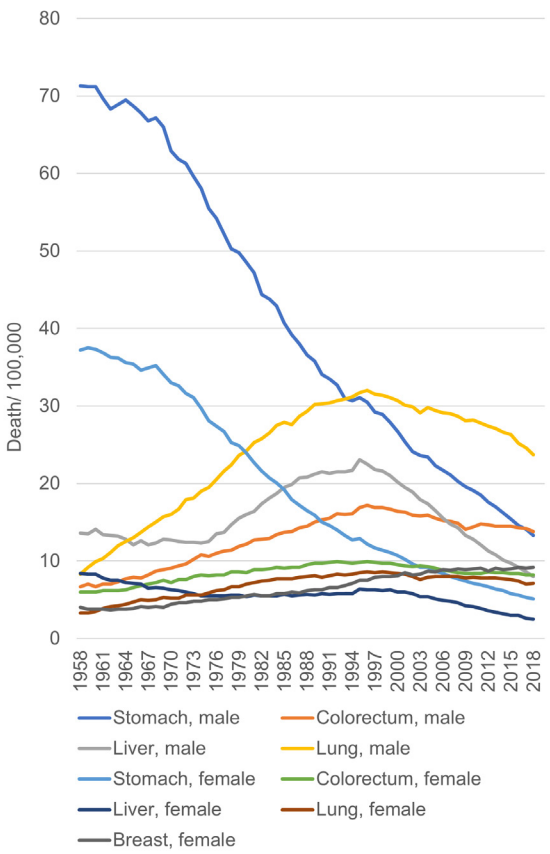

Figure 2. Trends in age-adjusted mortality rate of cancer of stomach, colorectum, liver, lung, and breast by sex in Japan, 1958-2018 (*3*). Gastric cancer showed a clear continuous decrease from 1960s in both male and female.

to improve both healthcare access and quality of health care across service areas and for all populations under universal health coverage by the public insurance system (*9*).

Despite a marked improvement in survival from gastric cancer in Japan through early detection, those who undergo surgical resection with systematic lymph node dissection and adjuvant chemotherapy, as well as patients with unresectable advanced or recurrent gastric cancer, have a poor prognosis. The development of more effective standard chemotherapies is therefore critical.

Prognosis in unresectable advanced or metastatic gastric cancer

The survival times from previous clinical trials for untreated advanced gastric cancer in Japan are generally better than those reported from trials in European and North or South American countries. The longer survival times of Japanese trials would be related to a higher proportion of patients having good prognostic factors such as a better performance status or prior gastrectomy (*10,11*) (Figure 4). Having a small tumor burden is also a good prognostic factor as well as subsequent chemotherapy after the failure of first-line treatment. A Korean phase III trial showed that the effect of second-line chemotherapy led to a slight improvement in post-progression survival and overall survival (OS) time (*12*). In particular, the survival times of East Asian patients with metastatic gastric cancer tended to be close to those of Japanese patients (*10,11,13*).

In AVAGST trial which was an international, randomized, placebo-controlled phase III study of chemotherapy with or without bevacizumab as first-line therapy for patients with advanced gastric cancer, the median duration of overall survival for patients treated with cisplatin 80 mg/m^2 plus capecitabine (1,000 mg/m^2 orally bid days 1-14) or 5-fluorouracil (5-FU) (800 mg/m^2/day continuous IV infusion days 1-5) every 3 weeks was 7.3 months (95% confidence interval (CI), 6.4-8.7) in Eastern Europe/South America, 9.1 months (95% CI, 6.9-14.4) in US/Western Europe, 11.6 months (95% CI, 9.1-15.6) in Korea and other Asian countries, and 14.1 months (95% CI, 10.9-17.6) in Japan. The hazard ratios (HR) for overall survival for each region when compared against US/Western Europe were 1.47 (95% CI, 1.09-1.99) for Eastern Europe/South America, 0.91 (95% CI, 0.67-1.25) for Korea and other Asian countries, and 0.87 (95% CI, 0.64-1.19) for Japan. Median progression-free survival by region was 4.4 months (95% CI, 4.0-5.4) in Eastern Europe/South America, 4.4 months (95% CI, 4.0-5.7) in US/Western Europe, 5.6 months (95% CI, 4.8-6.5) in Korea and other Asian countries, and 5.7

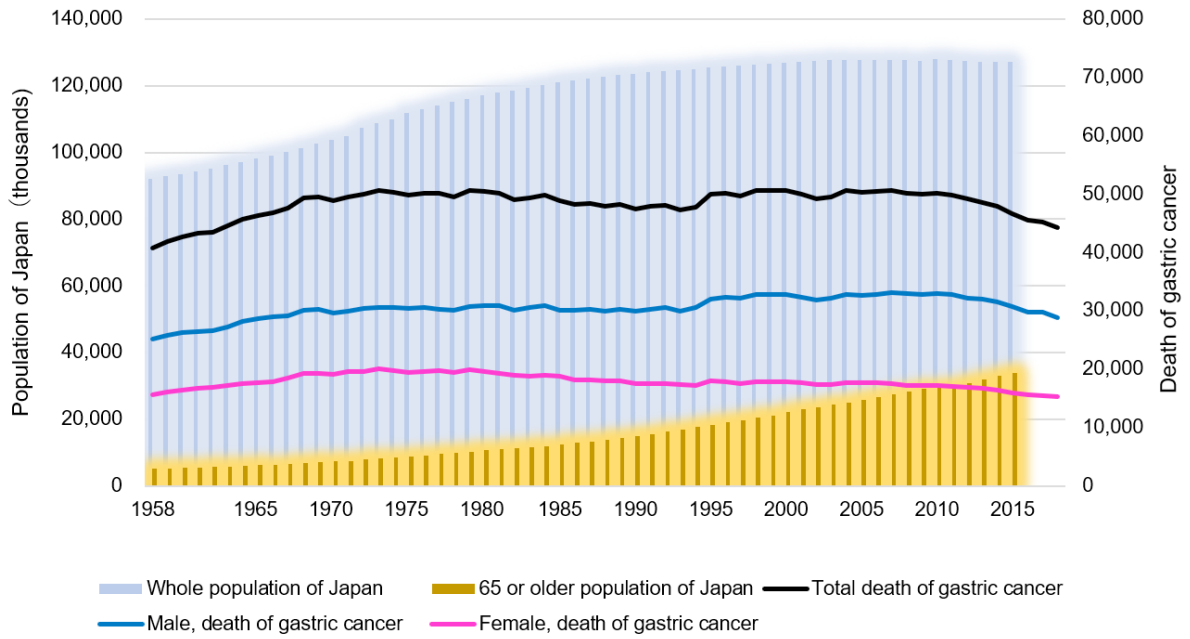

Figure 3. Trends in the number of death due to gastric cancer in Japan (*7,8*). The number of death due to gastric cancer has not decreased because of the increase of 65 or older population.

months (95% CI, 5.1-7.0) in Japan. Therefore, crucial trials of novel drugs should be undertaken mainly as East Asian trials rather than as global trials that include Central and Eastern European or South American countries (*10,11,13*). The final results for the latter would be expected to differ because the survival time of patients with gastric cancer in such countries were relatively shorter compared to those of patients in East Asian countries.

In recent global trials, the proportion of enrolled Japanese patients was capped at approximately 20% (*10,14,15*). However, this should be changed to decrease the ratio of patients entered into trials from European and American countries in order to identify drugs that specifically prolong the survival of Japanese and other East Asian patients. This is because of the difference in post-progression survival time after the failure of test treatments. The survival effect is also weakened in populations with longer survival times, resulting in different outcomes between East Asia and the rest of the world (*16*).

Standard first-line treatment in Japan

S-1 plus cisplatin (CS) is considered a standard first-line therapy based on the results of a randomized trial, Japan Clinical Oncology Group (JCOG) 9912, comparing oral S-1, a dihydropyrimidine dehydrogenase inhibitory fluoropyrimidine drug, with the continuous infusion of 5-FU and the SPIRITS trial, which highlighted the superiority of CS to S-1 in OS (*17,18*).

Globally, capecitabine plus cisplatin showed no inferiority to cisplatin plus 5-FU (*19*). Furthermore, oxaliplatin showed comparable activities to cisplatin in two phase III trials conducted in Europe (*20,21*). The Japanese G-SOX study also demonstrated comparable results in both progression-free survival (PFS) and OS between treatments with S-1 plus oxaliplatin (SOX) and CS (*22*). In the SOX regimen, S-1 was given orally for the first 2 weeks of a 3-week cycle, and oxaliplatin was infused at 100 mg/m^2 on day 1. In the CS regimen, S-1 was given for the first 3 weeks of a 5-week cycle, and cisplatin was administered at 60 mg/m^2 on day 8.

Thus, oral fluoropyrimidine plus platinum has been recognized worldwide as a standard chemotherapy for patients with human epidermal growth factor receptor 2 negative gastric cancer. Although significant differences in PFS and OS were not observed between elderly and non-elderly patients for SOX and CS, SOX showed better trends in PFS (HR, 0.805; 95% CI, 0.588-1.102) and OS (HR, 0.857; 95% CI, 0.629-1.167) compared with CS (*23*).

Management of chemotherapy in diverse patients

Regimens with cisplatin at more than 50 mg/m^2 have usually been administered as inpatient chemotherapy because these are highly emetic and require intensive hydration (*24*). However, cisplatin is known to be commonly administered as outpatient chemotherapy in other countries. This results in a decrease in the quality of life of patients and imposes a large financial burden due to the hospitalization cost.

The completion rate for two cycles of CS as an outpatient was found to be 78% (90% CI, 63-89), even in patients who were known to drink more than 1,500

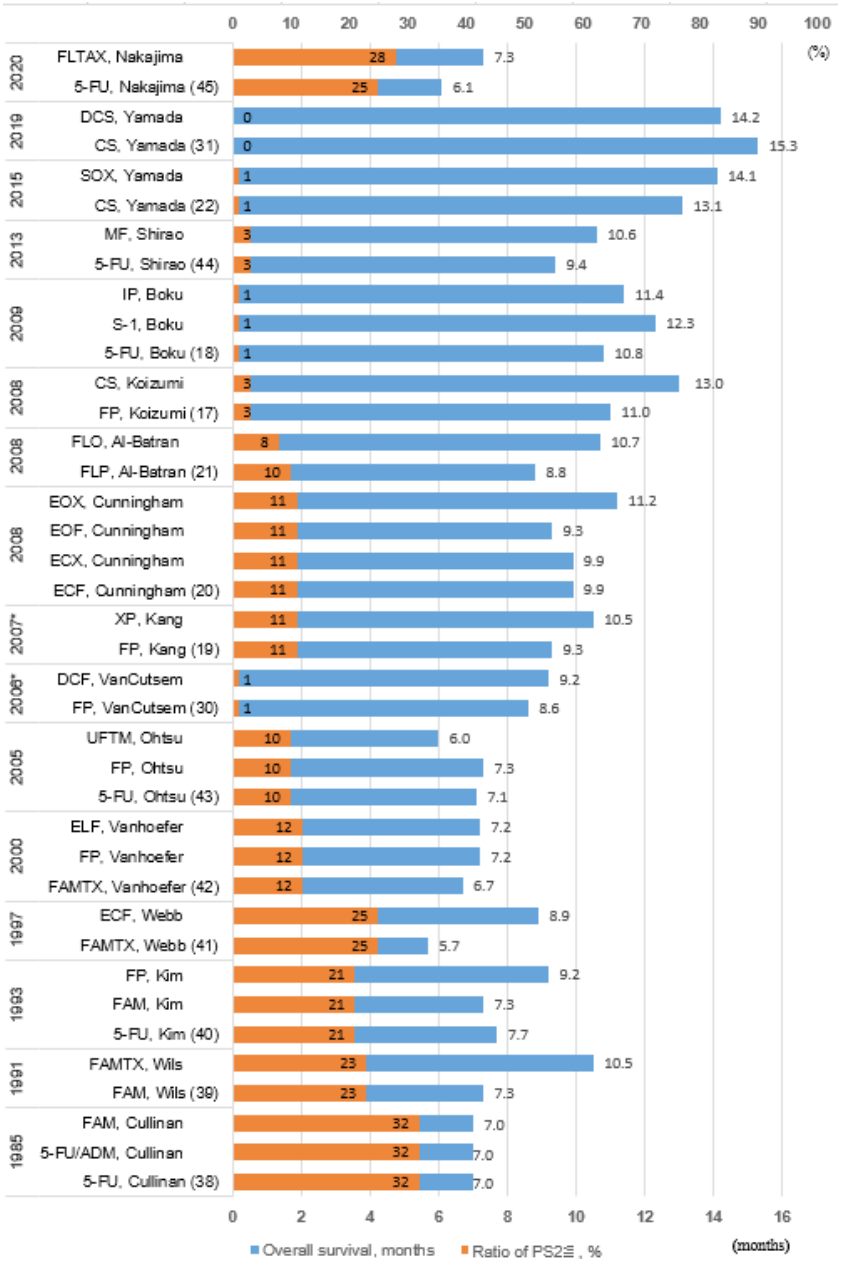

Figure 4. Overall survival of unresectable advanced/metastatic gastric cancer. The number of patients with poor performance 2 or more (*Karnofsky performance status < 80%) has decreased and the overall survival time has been over a year in recent trials. The target population was patients with peritoneal dissemination and/or ascites in articles doi: 10.1093/jjco/hyt114 and doi: 10.1007/s10120-020-01043-x. 5-FU, 5-fluorouracil; ADM, doxorubicin; CS, cisplatin/S-1; DCF, docetaxel/cisplatin/5-FU; DCS, docetaxel/cisplatin/S-1; ECF, epirubicin/cisplatin/5-FU; ECX; epirubicin/cisplatin/capecitabine; ELF, etoposide/leucovorin/5-FU; EOF, epirubcin/oxaliplatin/capecitabine; EOX, epirubicin/oxaliplatin/capecitabine; FAM, 5-FU/doxorubicin/mitomycin C; FAMTX, 5-FU/doxorubicin/methotrexate; FLO, 5-FU/leucovorin/oxaliplatin; FLP, 5-FU/leucovorin/cisplatin;FLTAX, 5-FU//-leucovorin/paclitaxel; FP, 5-FU/cisplatin; MF, methotrexate/5-FU; SOX, S-1/oxaliplatin; UFTM, tegafur/uracil/mitomycin C; XP, capecitabine/cisplatin.

mL per day before the start of CS therapy, in a feasibility study of relatively younger patients with advanced gastric cancer and a median age of 62 (range, 34 to 75). Of seven in 32 patients (22%) who did not complete the CS therapy, six continued CS as inpatient chemotherapy with intravenous hydration from the subsequent cycle. However, one was forced to switch to S-1 monotherapy due to grade 3 anorexia, nausea, and diarrhea. CS is not a feasible treatment for many elderly patients in an outpatient setting in clinical practice, while the number of patients who cannot tolerate CS in our rapidly aging society is increasing. Over time, the average age of death due to gastric cancer has increased from 61 years in 1950 to 73 in 2000 (*4*).

In addition, patients of working age require convenient therapy with mild toxicities that results in a short hospital stay, and at a lower cost. The Ministry of Labour, Health, and Welfare strongly supports the treatment of workers with cancer using anti-cancer agents by developing initiatives such as a "Plan to Accelerate Cancer Control Programs" in Dec. 2015 and subsequently a "Third Basic Plan to Promote Cancer

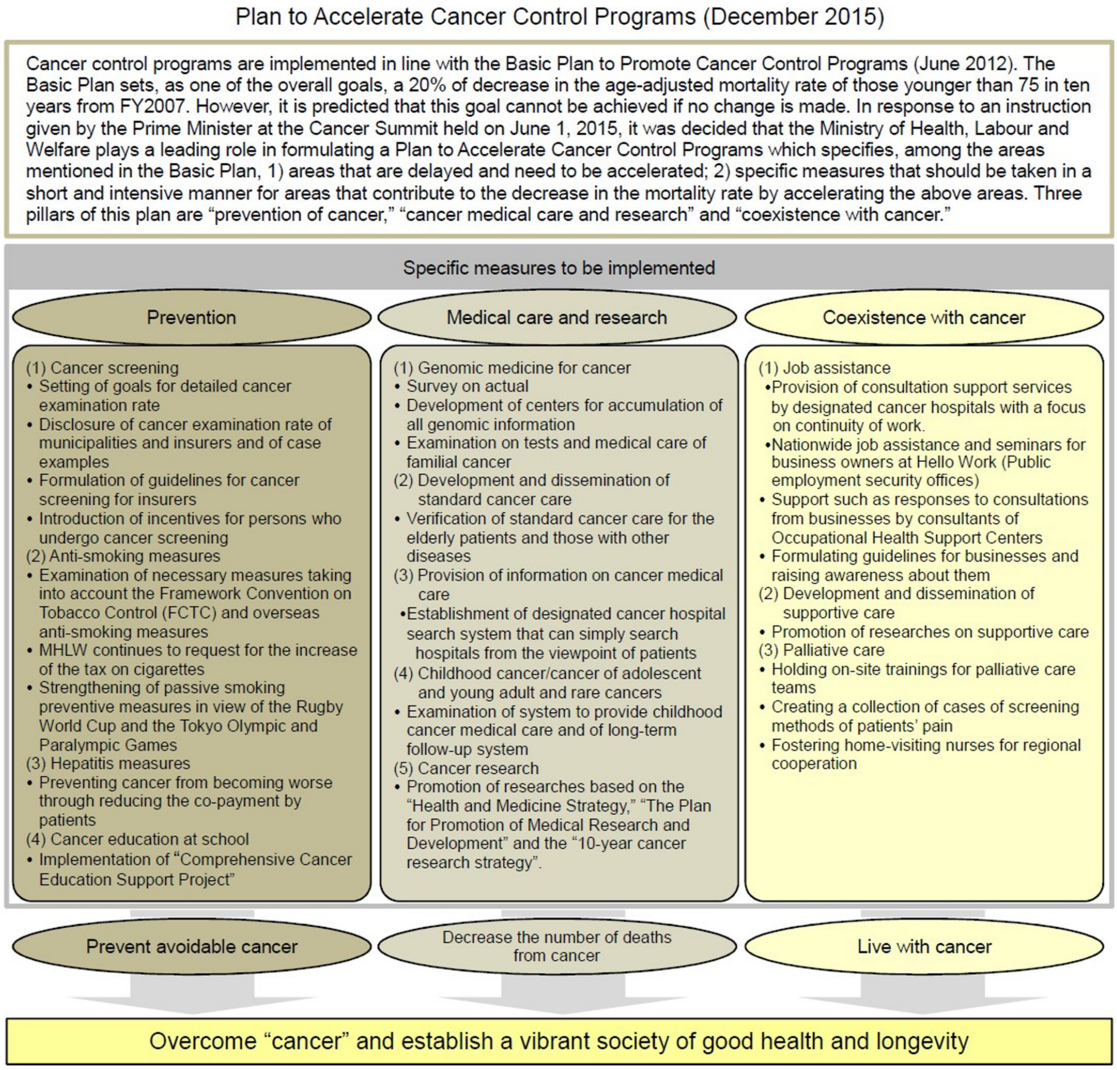

Figure 5. Plan to accelerate cancer control programs (*25,26*).

Control Programs", from Mar. 2018 (*25,26*) (Figure 5). The treatment of gastric cancer with SOX therapy, which does not require hydration, induces mild nausea and vomiting in patients that can be treated by maintaining their oral intake with adequate anti-emetic treatment usually given in our outpatient clinic.

Leukopenia, neutropenia, nausea, and vomiting during the first cycle of SOX treatment, then vomiting and stomatitis during the first cycle of CS were more frequently observed in female patients compared with males (*27*). On the other hand, a difference in drug efficacy was not observed between females and males undergoing either regimen. Therefore, intensive anti-emetic therapy with an aprepitant, consequent dexamethasone on day 2 to 3 and olanzapine should be considered, especially for females, because of the higher incidence of nausea and vomiting with SOX as well as high emetogenic chemotherapeutic agents (*28,29*). Sex differences in adverse reactions during SOX and CS therapies were confirmed in the G-SOX study and warrant further translational research studies to pursue the underlying cause.

Discontinued triplet therapy

The V325 study, which was mainly undertaken in European and American countries, demonstrated the superiority of triplet chemotherapy using docetaxel plus cisplatin and 5-FU (DCF) over doublet chemotherapy with cisplatin and 5-FU (CF) for patients with advanced gastric cancer (*30*). The median OS was 9.2 versus 8.6 months, and the regimen was associated with a risk reduction of 32%. The DCF regimen has not been accepted globally as a standard treatment due to its severe hematologic toxic effects (82% incidence of grade 3-4 neutropenia and 29% incidence of febrile neutropenia) and the small survival advantage.

In a randomized phase III study of Japanese patients with advanced gastric cancer known as JCOG1013 (*31*), the addition of docetaxel to cisplatin plus S-1 (DCS) was of no benefit to patients with advanced gastric cancer either for OS or PFS; the median OS was 14.2 versus

15.3 months (HR, 0.99; 95% CI 0.85-1.16; $p = 0.47$).

In a previous V325 study that revealed a survival benefit with triplet chemotherapy consisting of docetaxel, cisplatin and DCF, only 32% and 41% of patients received second-line chemotherapy in DCF and CF arms, respectively, from 1999 to 2003. However, 79% and 77% of patients received second-line chemotherapy in CS and DCS groups, respectively, in the JCOG1013 study from 2013 to 2016. It is thought that patient characteristics at baseline and during different treatment courses, including subsequent chemotherapy, between V325 and this study may be a major reason for inconsistent results. Recent phase III trials of chemotherapy versus chemotherapy plus ramucirumab, an anti-vascular endothelial growth factor receptor antibody, or pembrolizumab, an anti–programmed cell death protein 1 antibody, also did not reveal any survival benefit for biologics with regard to OS (*32-35*).

Future perspectives

Globally, capecitabine plus cisplatin has shown non-inferiority to cisplatin plus 5-FU in the treatment of advanced gastric cancer (*19*). Furthermore, oxaliplatin showed comparable activities to cisplatin in three phase III trials conducted in Europe and Japan (*20,21,22*). Thus, fluoropyrimidine plus platinum is still recognized as a standard chemotherapy worldwide. However, progress in the treatment of metastatic gastric cancer has been limited.

DNA repair systems allow cells to overcome the DNA damage induced by chemotherapy. DNA interstrand, intrastrand, and DNA–protein crosslinks caused by cisplatin are repaired by the nuclear excision repair pathway, of which excision repair cross-complementation group 1 (ERCC1) is an essential part. In the JCOG9912 trial involving patients with advanced gastric cancer, low ERCC1 expression was a significant independent favorable prognostic factor in those who received first-line chemotherapy regardless of treatment regimen (*36*). The mRNA expression of ERCC1 and dihydropyrimidine dehydrogenase in the diffuse type were higher than those in the intestinal type. Higher vascular endothelial growth factor-A expression was more commonly observed in patients with unresectable disease ($p = 0.060$), target lesions ($p = 0.052$), and liver metastasis ($p = 0.090$) (*36*). In an animal model, high ERCC1 expression led to cisplatin resistance and allowed cells to once again displace cisplatin from cellular DNA. Fluoropyrimidines can induce a variety of DNA damage in human cancer cell lines by a mechanism involving enzymes involved in DNA repair, as well as downstream factors such as p53. The expression of wild-type p53 was a strong predictor of sensitivity to 5-FU in cell lines of the National Cancer Institute's Anticancer Drug Screen panel *in vitro* (*37*). Thus, prevailing strategies used against metastatic gastric cancer need to be modified with regard to innovative treatments with current drugs and/or novel gene editing, keeping in mind each categorized population to be treated.

Conclusions

In a society of diversity including medical environment, culture, sex, comorbidities, even if the same treatment is performed, the outcome of the individual patient is different. It is important for each society to implement established treatment through clinical trials made in a similar medical circumstance like East Asia, knowing that the evidence from global trials aimed at drug approval does not necessarily show external validity. Further, individualization of treatment by reverse translational research by clinical specimens with sufficient clinical information is increasingly important in improving the treatment outcomes and QOL of individual patients.

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