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Oral Fluoroprimidine Based Chemotherapy of HER2 Positive Gastric Cancer

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Commentary

Gastric cancer (GC) is a heterogeneous cancer which mortality rate reported a third in Japan. Hence, we have occasionally experienced locally advanced GC with HER2 negative and positive which median survival time is approximately 6 to 13 months [1]. The treatment of advanced GC is chemotherapy. Actually, 5-fluorouracil had been a key drug against advanced GC. Japanese Clinical Oncology Group (JCOG) 9205 trial reported that cisplatin (CDDP) with 5FU proved superiority against 5FU alone [2]. In 1990's, the oral DPD-inhibitory fluoropyrimidine (tegafur, 5-chloro-2, 4-dihydroxypyridine and potassium oxonate) of S-1 had developed against gastrointestinal cancers. 5FU had replaced by S-1 which reasons are high antitumor effects and several adverse events, especially less gastrointestinal adverse events. In 2000's, S-1 plus CDDP (SP) chemotherapy was established against advanced GC by SPIRITS and JCOG9912 trial [3,4]. In the present situation, Japanese guideline recommends SP regimen against HER2 negative GC as a first line chemotherapy. Otherwise, we have occasionally experienced CDDP induced adverse events, such as renal dysfunction, hearing impaired, peripheral neuropathy and long hydration time. Hence, Japanese investigators reported oxaliplatin (L-OHP) and S-1 (SOX) therapy with advanced GC which revealed response rate of 59% in a phase II and 55.7% in a phase III, respectively [5,6]. Furthermore, Korean investigators reported that L-OHP and capecitabine (Cap) (CapeOX) and SOX therapies were equally active and well tolerated with advanced GC in phasestudy [7]. We previously reported that SOX clinical study with HER2 negative GC which response rate was 33.3% and disease control rate was 83.3% [8]. However, we have to consider HER2 positive GC. Japanese guideline recommends Trastuzumab (Tmab) combined CDDP and capecitabine (Cap) (XP) against HER2 positive GC because ToGA study revealed that Tmab combined group had met primary endpoint (Hazard Ratio 0.74) [9]. Furthermore, Japanese investigators reported a phase trial of HERBIS-1 study with Tmab combined SP [10]. Actually, we have experienced Tmab combined XP or SP chemotherapies, those chemotherapies were unfit for some GCs following as; senior patients, chronic kidney disease patients and outpatient unit. Furthermore, we have occasionally experienced Hand-Foot-syndrome due to Cap. Hence, we need alternative oral-fluoroprimidine chemotherapy plan. We considered to administer Tmab-SOX with advanced GC which reasons are following; a) Li et al. reported that Tmab-SOX was remarkable response of HER2 positive gastric cancer [9], b) Osawa et. al. reported that Tmab-SOX therapy demonstrated pathological complete response of synchronous liver metastasis of gastric cancer [11], c) Japanese phase II/III trial reported that SOX therapy was remarkable response of HER2 negative GC [5,6], d) we reported that efficacy and safety trial of SOX with GC [8]. Recently, an 80-year-old man who received Tmab-SOX therapy for solitary synchronous liver (S6) and lymph nodes metastasis of Esophago-gastric junction adenocarcinoma, which revealed diffuse type and HER2 score 3+ immunohistochemically (IHC). Although the heterogeneity of HER2 protein expression and *HER2* gene amplification within a same tumour is a common finding in GC, his uniform overexpression of HER2 protein had greater than 5.7-fold amplification of *HER2* gene. Tmab-SOX: (Tmab: 8 mg/kg for first cycle, 90 min and 6 mg/kg for subsequent cycles on day1, 30 min, L-OHP: 100 mg/m^2, day 1, 120 mins, S-1: 80 mg/m^2 twice daily, days 1 to 15, orally, every 3 weeks). The solitary liver metastasis shrunk from 52 mm to 34 mm, lymph-node metastasis shrunk from 36 mm to 22 mm and primary shrunk in endoscopic response 2 cycles later. We have been continuing Tmab-SOX therapy and the patient have not any complaints and adverse events in the present situation. However, Tmab with XELOX and SOX are convenient to treat for any GC patient even outpatients' units. Furthermore, we need alternative oral-fluoroprimidine chemotherapy plan such as adverse events which are Hand-Foot-syndrome with Cap and gastrointestinal toxicities with S-1. Finally, Tmab-SOX therapy proved remarkable response and might be an alternative chemotherapy plan against HER2 positive GC.

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