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Short Communication Open Access

A search for Optimal Cytotoxic Drug as a Partner for the Oral Fluoropyrimidines in the Postoperative Adjuvant Chemotherapy for Gastric Cancer

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Introduction

This short communication reflects the authors' report on feasibility of postoperative adjuvant chemotherapy with S-1 and cisplatin for gastric cancer [1]. In addition, this article summarizes the brief history and current status of the development of postoperative adjuvant chemotherapy in Asia and, in particular, in Japan.

Gastric cancer is characterized by aggressive biological behavior with high risk of recurrences, and treatment with surgery alone cannot be recommended unless the disease is diagnosed in the early stage. In Japan, efforts for early diagnosis through screening had long been considered as the essential step in improving the outcome, and the strategy of upfront surgery had been imperative. At the same time, surgeons established D2 dissection during the time when patients were relatively young, fit and lean, and excellent local control was the consequence. This meant that patients who nevertheless had recurrence suffered mainly from metastases to the distant organs and peritoneal surface. The Japanese investigators therefore opted for systemic postoperative chemotherapy as an adjuvant treatment to add on to surgery rather than radiation which can be regarded as another local treatment.

Given the adverse effects of gastrectomy, relative drug intensity tends to be superior when chemotherapy is delivered before surgery. In addition, tumor shrinkage as a consequence of preoperative treatment may enable a surgeon to resect a bulky locally advanced cancer more comfortably. On the other hand, ineffective preoperative treatment may result in disease progression, which might render barely resectable cancers decisively unresectable. This had been a greater concern in the days when response rates of chemotherapeutic regimens had not been as high as it is today. It is well documented that minimal residual disease after surgery are more vulnerable to systemic chemotherapy when compared with bulky diseases. Thus, the first evidence of adjuvant treatment for resectable advanced gastric cancer in Asia emerged as postoperative adjuvant chemotherapy [1] while the phase III evidences for the neoadjuvant strategy are yet to be established.

Patients with stage II/III gastric cancer in Japan are currently treated by S-1 (eight 6-week cycles of oral S-1 at 40 mg/m^2 twice daily on days 1-28 followed by 2 weeks of rest) for 12 months, based on a pivotal phase III trial that showed its benefit over surgery alone [1]. The hazard ratio (HR) for death at 5 years in that trial was 0.669 (95% confidence interval (CI) 0.540-0.828). Subset analyses revealed that the favorable effect of S-1 waned somewhat as the disease-stage advanced from Stage II to Stage IIIB. In the meantime, a phase III trial for advanced/unresectable gastric cancer revealed benefit of a S-1/cisplatin combination (5-week cycle of S-1 40 mg/m^2 twice daily on days 1-21 plus intravenous cisplatin 60 mg/m^2 on day 8) over S-1 as a single agent (HR for death, 0.77; 95% CI 0.61-0.98; p=0.04)[2]. These facts led the authors at Chubu Clinical Oncology Group (CCOG), a study group consisting mainly of community hospitals in the Aichi district, Japan, to attempt delivering the S-1/cisplatin combination postoperatively for a Stage III/IV population (the Stage IV population denotes patients with positive peritoneal cytology, minimal peritoneal deposits and those with a single or a small number of liver metastases that were co-resected) [3]. However, this attempt (CCOG0705 study) resulted in an utter failure due to the poor compliance, with only 7 of 31 patients (22.6%) being able to complete 5 cycles of S-1/cisplatin. The relative drug intensities of S-1 and cisplatin were 37% and 40%, respectively. Takahari et al. conducted another feasibility study to look at the compliance of 3 cycles of S-1/cisplatin (followed by single agent S-1 for a total of 12 months) postoperatively with Stage III gastric cancer [4]. In that study, the researchers that consisted of medical oncologists from four acclaimed cancer centers in Japan experienced similar difficulties as in the CCOG0705 and decided to amend the treatment regimen, whereby the patients were to be treated by one 6-week cycle of S-1 monotherapy before receiving the combination treatment. This increased a time interval between surgery and the first administration of cisplatin by 6 weeks, and the treatment completion rate for 3 cycles of S-1 and cisplatin improved from 57% to 81%. In addition, the outcome of Stage III patients treated in this study turned out to be excellent, with the 3-year recurrence-free survival rate of 74.1% (95% CI 60.8~83.5%, IIIA 81.8%, IIIB 64.0%) [5]. These results and availability of aprepitant, a new generation of antiemetic drugs, prompted us to conduct another feasibility study, CCOG1106 [6], to confirm that postoperative administration of the S-1/cisplatin combination is feasible even at community hospitals if the introduction of cisplatin is intentionally delayed. Completion rate of the treatment consisting of one cycle of S-1 followed by 4 cycles of S-1/cisplatin in CCOG1106 was 60.6%, and the relative dose intensities of S-1 and cisplatin were 77.3% and 72.3%, respectively. When four Stage IV patients whose treatment was discontinued due to rapid disease progression were excluded, the completion rate reached 69.0%, Although these data aroused interest of several researchers, the need for admission and intensive hydration when administrating cisplatin was considered a disadvantage in a society suffering from high medical cost and aging population. Thus, our long-standing efforts to deliver cisplatin after gastrectomy failed to develop into a phase III trial.

During the same period, attempts were made to incorporate taxanes with preferable toxicity profile regarding the gastrointestinal toxicity into postoperative adjuvant chemotherapy. A combination of S-1 and

docetaxel (3-week cycle of S-1 40 mg/m^2 twice daily on days 1-14 plus intravenous docetaxel 40 mg/m^2 on day 1) was found to be arguably superior to the S-1 monotherapy in the advanced/unresectable setting (HR for death, 0.84; 95%CI 0.71-0.99; p=0.032) [7]. Moreover, postoperative administration of 4 cycles of the same S-1/docetaxel combination was found to be quite feasible, with completion rate of 79.2% (95% CI 65.2~76.9) [8]. Thus, it was this combination that eventually found a way to a phase III trial with S-1 monotherapy as a control. This trial (the START-2 trial) was initiated in April 2013 and only patients with Stage III gastric cancer are eligible. The sample-size is 1,100 patients, of which just over 50% has been accrued as of December 2015.

It is important to mention that another phase III trial conducted in Korea and China has already proven superiority of a combination of capecitabine and oxaliplatin (XELOX: (3-week cycle of capecitabine 1,000 mg/m^2 twice daily on days 1-14 plus intravenous oxaliplatin 130 mg/m2 on day 1) given for 6 months over surgery alone (HR for death, 0·66; 95% CI 0·51-0·85; p=0·0015) [9]. Estimated 5-year overall survival was 78% (95% CI 74-82) in the adjuvant capecitabine and oxaliplatin group versus 69% (95% CI 64-73) in the observation group. Oxaliplatin had been unavailable in Japan for a long time until the government authorities finally approved the drug based on a phase III comparison in which non-inferiority of oxaliplatin against cisplatin in advanced/unresectable gastric cancer was formally proven [10]. A prospective study to look at feasibility and safety of postoperative XELOX in the Japanese population also generated satisfactory results, although relatively fit patients had been selected. Although it may be inadequate to make a direct comparison between the two independent randomized phase III trials, a simple comparison of hazard ratios does not suggest definite superiority of the doublet over the monotherapy. Therefore, S-1 is likely to remain the first-choice in the Japanese Gastric Cancer Treatment Guidelines, with XELOX arguably placed alongside it. If one considers S-1 as a key fluoropyrimidine in the treatment of gastric cancer, it can now be combined with oxaliplatin because such combination (SOX: 3-week cycle of oral S-1 at 40~60 mg twice daily on days 1-14 plus intravenous oxaliplatin 100 mg/m^2 on day 1; oxaliplatin starting from the second cycle) has also been explored in a feasibility study. Completion rate of a cycle of S-1 monotherapy followed by 7 cycles of SOX was 74.2%, and median relative dose intensities for S-1 and oxaliplatin were 77.1% and 72.6%, respectively [11]. The SOX regimen currently lacks in a phase III evidence, and will have to be ranked somewhere below S-1 monotherapy in the Japanese guidelines for the time-being. SOX will be explored in a new randomized trial launched by JCOG that explores neoadjuvant chemotherapy in a population of clinically Stage III gastric cancer.

It is worth noting that S-1 and XELOX have different characteristics in terms of the patterns of disease recurrence in curatively resected gastric cancer. Recurrences in the form of peritoneal carcinomatosis decreased significantly in the S-1 arm of the Japanese phase III trial, whereas the same drug had little impact on the incidence of hematogenous metastases. This phenomenon was robustly reproduced in another retrospective case series as reported from our institution [12]. On the other hand, XELOX significantly reduced recurrences through hematogenous/lymphatic routes, but did not effectively suppress peritoneal metastases [9]. Based on these observations, either of the two evidence-based treatments could now be selected where appropriate, depending on the estimated pattern of recurrence. In the meantime, accrual for the START-2 trial will be continued since its design had been to find a treatment that is superior to the S-1 monotherapy.

This article has looked exclusively at attempts to improve the outcome of gastric cancer patients in a forceful way, through adding another cytotoxic agent. However, there are other important aspects in the postoperative management of patients who underwent gastrectomy, given that the compliance of S-1 monotherapy was 87% at 3 months and 66% at 12 months postoperatively in the pivotal phase III trial [13]. Excessive loss in body weight [14], and lean body mass in particular [15], was shown to be a risk factor for poor compliance which in turn had a significantly negative impact on the patient survival. Instead of increasing the burden of cytotoxic agents, assisting the patients with minimally invasive surgery and rigorous nutritional support could be considered in the era of aging population.

Conclusion

To conclude, even using the states-of-the-arts antiemetic drugs, cisplatin is too toxic to be used as a standard treatment in the postoperative adjuvant setting. S-1 monotherapy will remain a standard, and a S-1/docetaxel combination is hoped to replace this. The recent emergence of oxaliplatin has provoked much dispute among the committee members of the Japanese guidelines, but theoretically, XELOX has sufficient evidence to be preferred in Stage III gastric cancer patients with particular risks for hematogenous metastases.

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