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Review

Chemotherapy in Elderly Patients with Gastric Cancer

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Abstract

Gastric cancer (GC) is one of the most frequent malignant diseases in the elderly. Systemic chemotherapy showed an improvement of quality of life and survival benefit compared to supportive care alone in patients with advanced GC. Because comorbidities or age-related changes in pharmacokinetics and pharmacodynamics may lead to higher toxicity, however, many oncologists hesitate to recommend elderly patients to receive chemotherapy.

Available data suggest that elderly patients with GC are able to tolerate and benefit from systemic chemotherapy to the same extent as younger patients. The age alone should not be the only criteria to preclude effective chemotherapy. However, proper patient selection is extremely important to deliver effective treatment safely. A comprehensive geriatric assessment (CGA) is a useful method to assess life expectancy and risk of morbidity in older patients and to guide providing optimal treatment. Treatment should be personalized based on the nature of the disease, the life expectancy, the risk of complication, and the patient's preference. Combination chemotherapy can be considered for older patients with metastatic GC who are classified as non-frail patients by CGA. For frail or vulnerable patients, however, monotherapy or only symptomatic treatment may be desirable. Targeted agents seem to be promising treatment options for elderly patients with GC considering their better efficacy and less toxicity.

Key words: Gastric cancer; Chemotherapy; Elderly; Review

Introduction

Gastric cancer (GC) is one of the most frequent malignant diseases, accounting for about 961000 new cases worldwide every year and the third leading cause of cancer-related death [1]. It is the fourth most common cancer behind lung, prostate, and colorectal cancer in men and the fifth most common cancer in women. GC is a disease of aging and its incidence increases gradually with age [2]. According to the Surveillance, Epidemiology, and End Results (SEER) database (http://seer.cancer.gov/csr/1975_2011), more than 60% of GC cases develop over the age of 65 and about one-third of patients are over 75 years. Although the incidence for new GC cases has been falling over the last decade, it is expected that the number of older patients with GC will increase significantly as population of the elderly is rapidly increasing all over the world. Thus, it becomes increasingly more important to understand how best to treat elderly patients with GC.

The majority of elderly patients with GC have locally inoperable or metastatic disease at presentation. It is well known that systemic chemotherapy has improved quality of life (QoL) and overall survival (OS) compared to supportive care alone in patient with advanced GC [3-5]. However, elderly patients tend to get undertreatment including less aggressive diagnostic evaluation, less aggressive surgery, and less intensive chemotherapy. Although age has not

been identified as a prognostic factor in the outcome of incurable advanced GC [6,7], many oncologists hesitate to recommend elderly patients to receive systemic chemotherapy because co-morbidities or age-related changes in pharmacokinetics and pharmacodynamics may lead to higher toxicity in the elderly. The lack of clear guideline is one of the important reasons for undertreatment in elderly patients with GC. Since many of clinical trials have imposed age limit for eligible patients and elderly patients have been under-represented in trials [8-10], treatment of elderly patients with GC could not be guided by current evidence from large phase III trials. Moreover, extrapolating results from middle aged adults to elderly patients who suffer co-morbidities and cognitive impairment can be dangerous.

Available data suggest that elderly patients with GC are able to tolerate and benefit from systemic chemotherapy to almost the same extent as younger patients [11,12]. Thus, the chronologic age, by itself, should not preclude the use of effective cancer treatment that can improve disease-free survival (DFS), QoL, or OS. The most important challenges of managing elderly patients with GC are to determine whether the expected benefit is superior to the risk of treatment and then to select most appropriate drugs or regimen. Taking into account comorbidities, performance status (PS), and geriatric functional status, we need to develop the ways to guide our decision-making as to the optimal therapy for elderly patients with GC. This review article is to analyze relevant trials including elderly patients with GC and to discuss an optimal strategy of chemotherapy for this special population.

Comprehensive geriatric assessment

The definition of an elderly patient varies according to social and economic situations. However, in most developed and developing countries, 65 or 70 years of age is commonly regarded as cut-off value. Aging is associated with a progressive reduction in functional reserve and an increased prevalence of chronic diseases as well as an increased incidence of cancer. Increased age is also related to changes in the pharmacokinetics and pharmacodynamics of cancer therapy and increased susceptibility to toxic complications [13]. For this reason, proper patient selection is extremely important to deliver effective anti-cancer treatment safely.

A comprehensive geriatric assessment (CGA) is a useful method to assess life expectancy and risk of morbidity and mortality in older patients [14-16]. It covers assessment of ability to self-care, mobility and risk of falls, comorbidities, polypharmacy, nutritional status, cognitive function, psychological status, social support, and geriatric syndromes. Structured CGA can detect subtle changes missed by traditional work-up and can be helpful to intervene patients' problems as well as to develop optimal treatment plan [17-19]. Based on the result of CGA, physicians can estimate the benefit and risk of anti-cancer treatment in the individual patient and provide personalized treatment.

Although CGA is recommended for all elderly patients aged more than 70 years, it may be time consuming and not be appropriate for all patients. Hurria *et al.* developed a brief CGA specific for elderly patients with cancer, Cancer-Specific Geriatric Assessment (CSGA) [20]. It assesses elderly patients using seven domains including functional status, comorbidity, polypharmacy, cognitive function, psychological status, social functioning and support, and nutritional status. CSGA can be self-administered and completed by most of elderly patients without assistance. Recent results from clinical trials demonstrated the feasibility of CSGA in predicting treatment-related toxicity in the elderly with cancers [21, 22]. Another way is a two-step approach using the Senior Adult Oncology Program 2 (SAOP2) screening tool presented by Extermann *et al.* [19]. This tool can be used to identify elderly patients who would benefit from a multidisciplinary geriatric evaluation.

Perioperative chemotherapy

The use of upfront chemotherapy may have several potential benefits including the early eradication of micrometastases, downstaging with improved chance of curative resection, high dose intensity of chemotherapy prior to the morbidity of surgery. Perioperative strategy emerged as an alternative treatment of care in patients with resectable GC since the MAGIC trial in 2006 [23]. The results showed that 5-year survival for patients received perioerative chemotherapy with epirubicin, cisplatin, and 5-FU (ECF) was significantly improved compared to those undergoing surgery alone [36% vs. 23%, P=0.009, hazard ration (HR)=0.75, 95% confidence interval (CI) 0.44 - 0.72]. In the subgroup analysis, there was no clear evidence of heterogeneity of treatment effect according to the site of the primary tumor, sex, the WHO performance status, or age group.

The French FNCLCC/FFCD trial compared perioperative chemotherapy and surgery alone in patients with resectable adenocarcainoma of the lower esophagus, gastroesophageal junction (GEJ), or stomach [24]. Chemotherapy consisted of two or three preoperative cycles and three or four postoperative cycles of cisplatin and 5-FU. Compared with the surgery group, the perioperative chemotherapy group had a better OS (5-year rate 38% vs. 24%, P = 0.02, HR

= 0.69, 95% CI 0.50 - 0.95); and a better disease-free survival (5-year rate 34% vs. 19%, *P* = 0.003, HR = 0.65, 95% CI 0.48 - 0.89). In the multivariable analysis, the favorable prognostic factors for survival were perioperative chemotherapy (P = 0.01) and stomach tumor localization (*P* < 0.01).

In a recent meta-analysis, neoadjuvant chemotherapy slightly improved the survival rate [odd ratio (OR) = 1.32, 95% CI 1.07-1.64, *P* = 0.01] in patients with AGC [25]. There were little or no significant differences of benefits between populations and regimens in the subgroup analyses. It also significantly improved the 3-year progression-free survival (PFS) (OR = 1.85, 95% CI 1.39 - 2.46, *P* < 0.0001), tumor down-staging rate (OR = 1.71, 95% CI 1.26 - 2.33, P = 0.0006), and R0 resection rate (OR = 1.38, 95% CI 1.08 - 1.78, P = 0.01). In addition, neoadjuvant chemotherapy did not significant increase operative complications (OR = 1.20, 95% CI 0.90 - 1.58, P = 0.21) or perioperative mortality (OR = 1.14, 95% CI 0.64 - 2.05, *P* = 0.65).

These results indicate that perioperative chemotherapy may significantly increase DFS and OS in patients with adenocarcinoma of the GEJ or stomach. However, the data available in elderly patients were very limited in this setting. With no prospective randomized studies, however, perioperative chemotherapy needs to be considered on an individual basis for elderly patients 70 years or older.

Adjuvant chemotherapy

Adjuvant chemotherapy following complete D2 gastrectomy has failed to show a significant survival benefit in patients with GC [26-27]. Recently, however, two large Asian randomized phase III trials (ACTS-GC trial and CLASSIC trial) demonstrated survival benefit of adjuvant chemotherapy after curative gastrectomy. The ACTS-GC trial in Japan enrolled 1059 patients with stage II or III GC who underwent gastrectomy with D2 lymph node (LN) dissection [28]. Patients were randomly assigned to receive adjuvant therapy with S-1 for 1 year or not after surgery. Adjuvant S-1 improved 3-year OS significantly with favorable toxicity and compliance (80.1% vs. 70.1%, HR = 0.68). The CLASSIC trial that was conducted in South Korea, Taiwan, and China evaluated the effect of adjuvant chemotherapy with capecitabine and oxaliplatin for patients with stage II–IIIB GC who received curative gastrectomy with D2 LN dissection [29]. In this study, 1035 patients were randomly assigned to receive adjuvant chemotherapy for 6 month or not. Adjuvant capecitabine and oxaliplatin improved 3-year DFS (74% vs. 59%, *P* < 0.001) compared to surgery alone for all stages (II, IIIA, and IIIB).

Five-year outcomes of these two trials were recently published [30, 31]. In ACTS-GC trial, S-1 adjuvant chemotherapy showed no significant improvement of 5-year DFS and OS in elderly patients aged 70 years or older [30]. However, a subgroup analysis of CLASSIC trial demonstrated that adjuvant chemotherapy improved 5-year DFS significantly but not OS for patients over 65 years of age [31]. Meta-analysis including these subgroup data confirmed that adjuvant chemotherapy improved DFS significantly (HR = 0.61, 95% CI 0.44-0.84), and OS marginally (HR = 0.75, 95% CI 0.55-1.01) in older patients. Therefore, adjuvant chemotherapy can be considered carefully for elderly patients with adequate organ function and PS who underwent curative surgery with D2 LN dissection.

Palliative chemotherapy

For patients with relapsed or metastatic GC, palliative chemotherapy can provide palliation of symptoms and improve QoL and OS compared with best supportive care [32]. Although the standard chemotherapy regimen has not yet been established, chemotherapeutic agents including older drugs [5-fluorouracil (5-FU), etoposide, mitomycin-C, anthracyclines, and platinums] [33-36] as well as newer drugs (capecitabine, S-1, irinotecan, paclitaxel, oxaliplatin, and docetaxel) [36-57] have demonstrated activity in patients with advanced EGJ adenocarcinoma or GC. Recently, target agents such as trastuzumab [58] and ramucirumab [59,60] have shown promising results in combination with cytotoxic regimens.

Cytotoxic chemotherapy

There are no randomized phase III trials that evaluated the efficacy and toxicity of chemotherapy in elderly patients with advanced GC. Instead, we can estimate indirectly the potential benefit of chemotherapy by two pooled analyses [11,12]. Trumper *et al.* performed a pooled analysis using three clinical trials conducted in the United Kingdom to determine to the benefit of palliative chemotherapy for advance esophago-gastric cancer in patients older than 70 years in comparison to younger patients [11]. Of 1080 patients enrolled into the trial, 257 (23.8%) were aged over 70 years. Among these elderly patients, 78 were aged between 75 and 79 years and 19 were 80 years or older. There were no significant differences in overall response rate (ORR), OS, and severe toxicity between two age groups, suggesting palliative chemotherapy is also useful for elderly patients without increased toxicities. In the multivariate analysis, moreover, the age itself (70 years or older versus less than 70 years) was not a prognostic factor for survival. Jatoi *et al.* also conducted a pooled analysis of eight consecutive

North Central Cancer Treatment Group (NCCTG) trials to investigate differences in adverse events and outcomes of palliative chemotherapy in older (≥ 65) versus younger (< 65) patients with metastatic esophageal cancer, EGJ adenocarcinoma, and GC [12]. Of 367 patients, 154 (41.9%) were aged over 65 years. Although severe adverse events were more frequently observed among elderly patients (73% vs. 66%, P = 0.02), survival outcomes (OS or PFS) were comparable in the both group. These results from the pooled analyses suggest that elderly patients can also benefit from palliative chemotherapy. However, the results also indicated that palliative chemotherapy should be administered with more caution under careful monitoring for severe toxicities. In addition, more tolerable regimens need to be developed for elderly patients with advanced GC.

Oxaliplatin, a third-generation platinum, is active against GC and has a favorable toxicity profile as compared with cisplatin. The combination chemotherapy of oxaliplatin with 5-FU or capecitabine for elderly patients has been investigated in phase II trials [39-45] and retrospective studies [46-48], using different doses and schedules. These studies indicated that oxaliplatin-based doublets were effective (ORRs of 34.9-52.5% and median OS of 9.0-10.5 months) and well tolerated in elderly patients. The REAL-2 trial, a randomized phase III study, compared oxaliplatin with cisplatin and capecitabine with 5-FU in 1003 patients with advanced esophagogastric cancer [37] and suggested that oxaliplatin and capecitabine were as effective as cisplatin and 5-FU. In a phase III trial by the German Study Group, 5-FU/leucovorin and oxaliplatin (FLO) and 5-FU/leucovorin and cisplatin (FLP) showed no significant differences in the median OS [38]. Interestingly, an unplanned subgroup analysis demonstrated that in patients older than 65 years, FLO resulted in significantly superior ORR (41.3% vs. 16.7%), time to treatment failure (5.4 vs. 2.3 months), and progression-free survival (PFS, 6.0 vs. 3.1 months), and an improved OS (13.9 vs. 7.2 months) as compared with FLP. Moreover, FLO was associated with significantly less toxicity than FLP. As a result, elderly patients treated with FLP discontinued treatment much earlier for toxicity or patients' request (after 1.7 vs. 3.3 months) and had shorter treatment duration (2.1 vs. 5.2 months). Although the results of unplanned subgroup analysis have limitations, oxaliplatin can be a more favorable partner than cisplatin in elderly patients. At present, therefore, the judicious use of oxaliplatin-based doublet seems to be reasonable when combination chemotherapy is considered for elderly patients with advanced GC.

Docetaxel is also an active drug in advanced GC. Al-Batran *et al.* performed randomized phase II trial to determine if docetaxel-based triplet is feasible in elderly patients with esphago-gastric cancer [49]. Patients were randomly assigned to receive 5-FU/leucovorin, oxaliplatin, and docetaxel (FLOT) or the same regimen without docetaxel (FLO). Triple combination (FLOT) improved ORR and PFS in locally advanced subgroup and in patients aged between 65 and 70 years but not in metastatic subgroup or in patients 70 years or older. Moreover, FLOT was associated with more treatment-related grade 3 or 4 adverse events (81.9 % vs. 38.6%, P < 0.001) and deterioration of QoL. These results suggest that triplet regimen including docetaxel should not be recommended for elderly patients with metastatic GC.

Oral fluoropyrimidines

Although 5-FU still has an important role in the treatment of GC, it tends to be substituted progressively with an oral fluoropyrimidine such as capecitabine or S-1. Capecitabine was compared with 5-FU in large two randomized non-inferiority trials [37,50]. The REAL-2 trial demonstrated that the HR for death in the capecitabine group was 0.86 (95% CI 0.80-0.99) compared to 5-FU [37]. The ML17032 trial by Kang *et al.* was a similar non-inferiority trial comparing capecitabine plus cisplatin (XP) versus 5-FU plus cisplatin (FP). In this trial, XP was confirmed as a viable alternative to FP, demonstrating non-inferiority [50. A pooled analysis of 1318 patients from the REAL-2 and ML17032 trials suggested that capecitabine-based combinations were superior to 5-FU based combinations in terms of OS and ORR [51]. S-1 was also compared to 5-FU in two randomized trials [52,53]. A trial by Boku *et al.* showed that S-1 was non-inferior to 5-FU as monotherapy and more convenient [52]. The FLAGS trial demonstrated that cisplatin plus S-1 was as effective as cisplatin plus 5-FU with a significantly improved safety profile [54]. Therefore, capecitabine and S-1 can replace 5-FU for treatment of patients with GC.

Recently the interim results of a phase III trial comparing capecitabine (X) and capecitabine plus oxaliplatin (XELOX) in elderly patients with AGC were reported [55]. Patients with chemotherapy-naïve, measurable AGC, aged 70 years or older were randomized 1:1 to receive X (capecitabine 1,000 mg/m^2 bid on day 1-14) or XELOX (X plus oxaliplatin 110 mg/m^2 iv on day 1). Median PFS was significantly longer in XELOX arm than in X arm (7 vs. 3 months, HR = 0.33, 95% CI 0.17-0.64). OS was also longer with XELOX (14 vs. 6 months, HR = 0.60, 95% CI 0.29-1.23). In addition, XELOX did not increase toxicities compared with X monotherapy. These results suggest that this regimen can be considered for elderly AGC patients with good PS.

Single agent chemotherapy with an oral 5-FU

The meta-analysis by Wagner et al. analyzed the data of 1914 patients from thirteen trials and demonstrated a statistically significant survival benefit of combination chemotherapy versus intravenous 5-FU monotherapy (HR = 0.82, 95% CI, 0.74-0.90) [32]. Considering toxicities of combination regimens, however, single agent chemotherapy with an oral 5-FU may be a useful option in elderly patients with advance GC. Lee *et al.* conducted randomized phase II trial to evaluate the efficacy of capecitabine or S-1 in patients aged more than 65 years [54]. Ninety-one patients were enrolled and most of them had ECOG PS 0 or 1 (93.4%) and Charlson comorbidity index 0 or 1 (94.5%). Both agents showed similar activity in elderly patients with advanced GC (ORR of 28.9% with S-1 and 27.2% with capecitabine). Both capecitabine and S-1 were well tolerated, and there were no significant differences in toxicities except more frequent hand-foot syndrome and stomatitis with capecitabine.

Koizumi *et al.* reported the results of phase II trial of S-1 monotherapy for patients aged 75 years or more (median, 80 years) with advanced GC [56]. S-1 achieved ORR of 21.2%, median PFS of 3.8 months, and median OS of 15.7 months with low frequencies of serious adverse events. The prolongation of OS might result from the minimal adverse events of S-1 which could preserve QoL and allow more than half of the patients to proceed to second-line treatment. Petrioli *et al.* investigated the safety profile of continuous oral capecitabine in patients 75 years or older with metastatic colorectal and GC who were considered ineligible for combination chemotherapy [57]. Capecitabine was administered at a fixed dose of 2000 mg daily without interruptions. Most of common toxicities were grade 1 or 2 and no serious hematologic toxicities were observed. Of 7 patients with GC, three had PR or SD. Based on these results, capecitabine or S-1 monotherapy can be a reasonable option for elderly patients who are too frail to tolerate combination chemotherapy.

Targeted therapy

There are limited but growing data available on the toxicity, safety and efficacy of targeted therapies in elderly patients with advanced GC. The ToGA trial by Bang *et al.* randomized 594 patients with HER2-positive metastatic GC or EGJ adenocarcinoma to receive a fluoropyrimidine (5-FU or capecitabine) and cisplatin with or without trastuzumab [58]. The addition of trastuzumab to chemotherapy resulted in a significant improvement of median OS (13.8 vs. 11.1 months, HR = 0.74, P = 0.046). A subgroup analysis showed the beneficial effect of trastuzumab remained in the old age group (≥ 60), with similar rate of severe toxicities. Therefore, trastuzumab in combination with chemotherapy should be considered for elderly patients with HER2-positive advanced GC.

Ramucirumab, a monoclonal antibody VEGFR-2 antagonist, has yielded promising results in the treatment of patients with previously treated advanced or metastatic GC or EGJ cancer in phase III trials as single agent or combination with paclitaxel [59,60]. REGARD trial demonstrated a survival benefit of ramucirumab compared to placebo (5.2 vs. 3.8 months, HR = 0.776, P = 0.047) [59]. Although hypertension was more commonly observed in the ramucirumab group, rates of other adverse events were mostly similar between the two groups. RAINBOW trial randomized 665 patients to receive paclitaxel with or without ramucirumab in patients with metastatic GC or EGJ adenocarcinoma showing progression on first-line chemotherapy [60]. Among 330 patients in ramucirumab arm, 126 patients (38%) were aged more than 65 years. Ramucirumab plus paclitaxel significantly increased median OS compared with placebo plus paclitaxel (9.6 vs. 7.4 months, HR = 0.807, P < 0.001). In the subgroup analysis, ramucirumab prolonged median OS similarly among patients aged 65 years and older (10.7 vs. 8.7 months, HR = 0.86) and among younger patients (9.3 vs. 7.1 months, HR = 0.75). Favorable findings were also the same for median PFS, with the benefit seen in the older group (4.6 vs. 2.9 months, HR = 0.67, P = 0.006), roughly matching that in the younger one (4.3 vs. 2.8 months, HR = 0.57, P<0.0001). Relative to placebo, however, ramucirumab was associated with a higher rate of grade 3 or 4 neutropenia in both age groups. Among patients aged 65 years or older, the rate was 49% with drug versus 24% with placebo; among younger patients, it was 36% and 16%, respectively. These results suggest that ramucirumab or ramucirumab plus paclitaxel can be useful salvage options in elderly patients with metastatic GC.

Conclusion

Although GC is one of the leading causes of cancer-related in the elderly, there is a paucity of prospective data on chemotherapy for elderly patients with GC. Thus, we are obliged to depend on the results of retrospective subset analyses of prospective trials and small phase II trials. Based on the available data, it seems clear that adjuvant or palliative chemotherapy is as effective in elderly patients with GC as younger patients if it is administered with more caution under careful monitoring for severe toxicities. However, proper selection of patients is extremely important and the optimal treatment for each patient should be guided by CGA.

Adjuvant chemotherapy (S-1 or capecitabine

plus oxaliplatin) can be considered carefully for elderly patients with adequate organ function and PS. When combination chemotherapy is considered for the elderly with advanced or metastatic GC, the judicious use of oxaliplatin plus 5-FU/leucovorin or capecitabine seems to be reasonable. For frail elderly patients, however, monotherapy with capecitabine or S-1 may be an optimal option. Targeted therapy appears to be promising in the elderly considering better efficacy and favorable toxicity. Finally, prospective clinical trials for especially elderly patients are needed to define the optimal guidelines of chemotherapy in the elderly with GC.

Competing Interests

The authors have declared that no competing interest exists.

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