REVIEW

Chemotherapy in older adults with gastrointestinal cancer : Current practices and future directions in Japan

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Abstract : Chemotherapy for cancer has significantly improved owing to the increasing number of effective chemotherapeutic agents and supportive care. Recently, the number of older cancer patients has rapidly increased owing to the aging of the global population. However, in most cases, it is difficult to treat those using similar dosages or schedules as that of younger patients because older patients generally have unfavorable factors, such as decreased performance status and physical and cognitive conditions, thus increasing the incidence of complications and side effects. Chemotherapy for gastrointestinal cancers has made significant progress in recent years with the introduction of molecular-targeted agents and immunotherapy. However, clinical trials showed limited evidence regarding the efficacy of chemotherapy in older cancer patients, accounting for half of all patients, making it difficult to develop a well-established treatment strategy. This review aimed to evaluate the current state of chemotherapy for gastrointestinal cancer in older adults. Furthermore, the limitations and future perspectives were discussed. J. Med. Invest. 69 : 25-30, February, 2022

Keywords **:** *gastrointestinal cancer, chemotherapy, elderly*

INTRODUCTION

There is growing interest in the treatment of older adults with cancer. However, there is insufficient evidence from large-scale studies to be reflected in these guidelines. Therefore, the recently published "Japanese gastric cancer treatment guidelines 2021" : (1) strongly recommend chemotherapy for older patients with unresectable advanced or recurrent gastric cancer in good condition (fit), and otherwise recommends appropriate treatment options, including no treatment, based on the patient's condition. Meanwhile, the "Clinical practice guidelines of cancer drug therapies for elderly patients," which were first published in Japan in 2019, (2), reflecting the actual clinical practice, suggest the use of oxaliplatin instead of oral fluoropyrimidine and cisplatin. On the contrary, the results of the GO2 study, the first phase III study to evaluate the efficacy of low-dose chemotherapy regimens in older adults, were recently reported from the United Kingdom, demonstrating that reducing the intensity of oxaliplatin plus capecitabine (OX therapy) can improve patients' quality of life without significantly affecting the antitumor response (3). This result may have a significant impact on future treatment of gastric cancer in elderly patients.

The avastin in the elderly with xeloda (AVEX) trail in colorectal cancer reported that bevacizumab in combination with capecitabine improved the progression-free survival (PFS) (4), and phase II trials of various regimens using bevacizumab in combination with various anticancer agents, as well as regorafenib and trifluridine/tipiracil (FTD/TPI), which are relatively well tolerated, are underway. Therefore, the "Clinical practice guidelines of cancer drug therapies for the elderly" only suggest the use of bevacizumab in the initial chemotherapy of older patients with unresectable advanced colorectal cancer. By contrast, the NORDIC9 study reported the efficacy of the combination of S-1 and oxaliplatin at a reduced dose compared with that of the full dose of S-1 (5), which may indicate that combination therapy should be administered at an appropriately reduced dose, as in the case of gastric cancer. Although the existing evidence is still limited, immune checkpoint inhibitors (ICIs) are considered promising options for older patients with gastrointestinal cancer, given the accumulating clinical evidence. Various guidelines recommend that the indication and evaluation of chemotherapy for older patients should be determined through geriatric assessment (GA). In the future, high-quality clinical trials that not only evaluate the overall survival (OS), but also incorporate important indicators for older cancer patients, such as quality of life and functional status, should be conducted. In this review, we aimed to describe the current state of chemotherapy for older patients with gastrointestinal cancer and discuss the future perspectives.

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1) FUNCTIONAL ASSESSMENT OF OLDER PATIENTS IN CANCER TREATMENT

The aging population in Japan is rapidly progressing, and the proportion of people aged 65 years and older (aging rate) has now reached a new all-time high of 29.1%. The aging process differs greatly from person to person, and older people of the same age do not necessarily have the same physical condition. Therefore, treatment should be based on the individual's health conditions. However, conventional PS measurement methods, such as the Eastern Cooperative Oncology Group (ECOG) scale, are inadequate methods for assessing the physical status of elderly patients as they do not take into account the comorbidities and frailty (1). Geriatric functional assessment (GA) is a well-established series of standardized tests in the general practice that assesses physical performance, comorbidities, cognition,

medications, nutritional status, functional status, mental health, and social status of elderly patients. GA is recommended by the American Society of Clinical Oncology (ASCO) (6) and Japanese guidelines (1,2) because of its potential usefulness in detecting unrecognized problems, determining the appropriate treatment strategies, and predicting adverse events and prognosis when initiating chemotherapy in elderly cancer patients. However, it remains unclear whether GA-based interventions can reduce the incidence of chemotherapy-related adverse events. Therefore, Li *et al*. evaluated whether geriatric assessment-driven intervention (GAIN), a functional assessment intervention for the elderly, could reduce the risk of adverse effects of chemotherapy in elderly cancer patients (7). A total of 613 patients with solid tumors aged 65 years and older in the United States, including gastrointestinal cancers (33.4%), underwent GA and were randomized on a 2 : 1 basis to either GAIN (intervention) or standard of care (SOC) group. In the SOC group, the GA results were reviewed by an oncologist during caregiving. Results showed that the incidence rates of chemotherapy-related side effects of grade 3 or higher (graded using National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE],version 4.0) were 50.5% (95% confidence interval [CI] 45.6%–55.4%) in the GAIN group and 60.6% (95% CI 53.9%–67.3%) in the SOC group, a significant reduction of 10.1% (95% CI −1.5% to −18.2 % ; P = .05 ; 18.2% ; P = 0.02). Thus, the introduction of multidisciplinary GAIN significantly reduces the incidence of grade 3 or higher adverse events in the treatment of elderly cancer patients ; therefore, further investigation is required to confirm this result.

2) RECENT TRENDS IN CHEMOTHERAPY FOR ELDERLY PATIENTS WITH GASTRIC CANCER AND ESOPHAGEAL CANCER

In Japan, the incidence of gastric cancer by age group (2018) peaked in the 85–89 age group for both men and women. Approximately 65% of all patients with gastric cancer are aged >70 years (8). These elderly gastric cancer patients are rarely included in phase III clinical trials ; thus, only limited data are available. Therefore, most of the findings have been obtained from age-specific subgroup analyses and retrospective analyses of elderly patients. The recently published "Japanese Gastric Cancer Treatment Guidelines, Revised July 2021, 6th Edition" proposed the following clinical question : Is chemotherapy recommended for elderly patients with unresectable advanced or recurrent gastric cancer? This study reported that none of the previous research had a high level of evidence showing the efficacy of chemotherapy in elderly patients with advanced unresectable gastric cancer (search through September 2019). Therefore, after careful evaluation, the committee strongly recommends chemotherapy if the patient's condition is stable (fit). In other cases (vulnerable/unfit), the committee cannot make a clear recommendation considering various situations of elderly patients and recommends an appropriate treatment according to the patient's condition, including best supportive care. In addition, the committee pointed out the need to verify the usefulness of comprehensive geriatric assessment in the future.

In a subgroup analysis of a randomized phase III study (G-SOX) comparing SOX (S-1 + oxaliplatin) and CS (cisplatin + S-1), the efficacy and safety were compared in patients aged ≥70 years and those aged <70 years. In patients aged ≥ 70 years, SOX was non-inferior to CS (9), and the hematologic and gastrointestinal toxicities tended to be stronger with cisplatin.

Accordingly, the "Clinical Practice Guidelines of Cancer Drug Therapies for the Elderly" (literature search up to March 2017) (2) recommended that cisplatin should not be used in elderly patients with human epidermal growth factor receptor 2-negative unresectable advanced recurrent gastric cancer, while oxaliplatin should be used in combination with oral fluoropyrimidine.

Recently, in the United Kingdom, the results of the GO2 trial, the first phase III trial to evaluate the efficacy of low-dose chemotherapy regimens in the elderly, were reported (10). This study aimed to address the following clinical questions : Is reduced-dose palliative chemotherapy effective for patients with advanced esophageal and gastric cancers who are too old or too old to be eligible for potent therapy, and can GA help determine the best course of treatment? The results of this study demonstrated that lowering the intensity of chemotherapy can improve patients' quality of life without significantly impairing cancer control. They also found that baseline frailty, quality of life, and neutrophil/lymphocyte ratio (inflammatory marker) are predictive of the outcomes and thus contribute to guiding the treatment decisions. The main eligibility criterion for this study was the oncologist's judgment that the patient was too old or frail to be suitable for the full dose of standard combination chemotherapy, but not the commonly used criteria of PS, age, and comorbidities. The primary endpoint was PFS of OX (oxaliplatin plus capecitabine) therapy, while the secondary endpoint was the non-inferiority of the lower dose group to the 100% dose group in terms of OS. Frailty was examined using the baseline GA and nine assessment domains, and those who fell into three or more categories were judged to have severe frailty.

The study introduced a new end point, overall treatment utility (OTU), which assesses the overall treatment utility (including imaging, clinical symptoms, patient satisfaction, tolerability, and quality of life using the EORTC QLQ-C30) at 9 weeks in the reduced-dose group. This was an unprecedented attempt to incorporate the evaluation of the efficacy and tolerability of treatment as well as the value and acceptability of the treatment by the patients themselves. A good OTU requires the absence of cancer progression on imaging examination, any significant side effects, significant deterioration in quality-of-life (QOL), and adverse response to the patient's value/acceptability question. Poor OTU is characterized by cancer progression on imaging examination, one or more items with low value/acceptability, or patient mortality.

In 2014–2017, 512 patients were enrolled from 61 sites in the United Kingdom, of whom 170 were assigned to the 100% dose group, 171 to the 80% dose group, and 173 to the 60% dose group. The overall median age was 76 (51–96) years, 75% of the patients were men, 31% of the patients had an ECOG PS ≥2, and 58% of patients were judged to have severe frailty. The three groups were well balanced in terms of baseline characteristics. The PFS times were 4.9, 4.1, and 4.3 months, respectively. The 80% dose group (hazard ratio [HR] 1.09, 95% CI 0.89–1.32) and the 60% dose group (HR 1.10, 95% CI 0.90–1.33) were confirmed to be non-inferior to the 100% dose group (predefined non-inferiority margin : 1.34). No significant difference was observed in the OS (7.5 months vs. 6.7 months vs. 7.6 months) among the three study groups. At 9 weeks, more "good" OTUs and fewer "poor" OTUs were observed in group C than in group A (odds ratio [OR] 1.24, 95% CI 0.84–1.84). With regard to quality of life, no change was observed in group A, but groups B and C showed an improvement at 9 weeks of treatment compared with that before the initiation of treatment. The incidence of toxicity tended to be lower in the reduced-dose groups (groups B and C), while the duration of treatment tended to be higher in the reduced-dose group as the number of treatment cycles increased. Multivariate analysis showed that baseline frailty, quality of life, and neutrophil/lymphocyte ratio were independently associated with OTUs, and

these factors could be used to calculate the predictive scores. If a patient with a score of 1 was assigned to level C, he or she has a 68% probability of having a good OTU, a 20% probability of having a moderate OTU, and a 12% probability of having a poor OTU ; however, if the same patient was assigned to level A, he or she has a 41% probability of having a good OTU, 30% probability of having a moderate OTU, and 29% having a poor OTU.

Although these results were only obtained after evaluating OX therapy and will not necessarily hold true in the future with the introduction of more well-tolerated novel agents such as ICIs, they indicated that the goal of palliative chemotherapy in the elderly can be achieved using doses that are much lower than that of the current standard, without compromising antitumor efficacy.

Furthermore, the baseline GA can be used as a tool to determine the OTUs after treatment, which will assist physicians in identifying the necessity of chemotherapy and help patients in understanding the need for undergoing chemotherapy. The use of OTUs, which reflects the balance between benefits and harms, goes beyond the traditional outcome models of survival and toxicity and is expected to be used in various studies in the future. In addition, the results of this study suggest that lower doses of combination chemotherapy may be effective in younger frail patients, as opposed to the conventional view that higher dose is better if it is well tolerated.

3) CURRENT TRENDS IN CHEMOTHERAPY FOR ELDERLY PATIENTS WITH UNRESECTABLE ADVANCED RECURRENT COLORECTAL CANCER

In the last two decades, the prognosis of patients with unresectable colorectal cancer has been dramatically improved owing to the appropriate use of cytotoxic anticancer agents and molecular-targeted therapies. However, the increased incidence of hematological toxicity associated with fluoropyrimidine treatment in elderly patients and peripheral neuropathy caused by oxaliplatin treatment, which may decrease QOL, remains a concern. To date, the medical research council fluorouracil, oxaliplatin and irinotecan : use and sequencing (MRC FOCUS) 2 trial (11) has reported that capecitabine plus a reduced dose of oxaliplatin does not prolong the PFS. However, the AVEX trial reported that treatment with capecitabine plus bevacizumab improved the PFS (4), although it should be noted that there was an increased risk of developing grade 3 or higher thromboembolism. Based on the "Guidelines for the Pharmacotherapy of Cancer in the Elderly" (literature search up to March 2017) (2), the following clinical question was raised : "Is the use of bevacizumab recommended in the first-line chemotherapy of elderly patients with unresectable advanced recurrent colorectal cancer?" They concluded that bevacizumab is recommended as first-line chemotherapy because randomized control trials have shown that bevacizumab prolongs PFS, and the major adverse events, such as proteinuria and hypertension, are relatively easy to manage and have little impact on patients' QOL. Although the risk of developing grade 3 or higher thromboembolism is small, its impact on QOL is relatively large, thus suggesting the need to select patients according to their risk. The possibility of prolonging OS and PFS when bevacizumab is combined with anticancer agents other than capecitabine, other angiogenesis inhibitors, and anti- epidermal growth factor receptor (EGFR) antibody agents should be confirmed in future clinical trials.

As an alternative bevacizumab combination regimen, Ohta *et al*. conducted a phase II study (OGSG 0802) to evaluate the efficacy and safety of weekly bevacizumab plus 5-FU and leucovorin in patients aged >65 years with unresectable colorectal cancer (12). Forty-one patients were enrolled in the study ; the ORR was 36.6% (95% CI 22.1%–53.1%), the median PFS was 9.4 months (95% CI 7.4–17.7 months), and the median OS was 24.0 months (95% CI 19.9 months, not reached). Grade 3 or higher adverse events included neutropenia (24%), anorexia (10%), leukopenia (7%), and mucositis/stomatitis (7%), but no treatment-related deaths were reported (graded using NCI-CTCAE, version 4.0), suggesting the efficacy and tolerability of this regimen in elderly patients.

However, there is a lack of evidence to support the use of reduced doses of drugs in elderly patients in clinical practice. Winther *et al*. reported the results of the NORDIC9 trial, which investigated the combination of reduced doses of S-1 and oxaliplatin (5) and showed that a reduced dose can improve the PFS without increasing the risk of toxicity. The study was a randomized, open-label phase II trial conducted in Northern Europe and included patients aged 70 years or older with previously untreated metastatic colorectal cancer who were not candidates for full-dose combination chemotherapy. One hundred and sixty patients were randomized to receive full-dose S-1 (30 mg/m^2) followed by second-line treatment with irinotecan at the time of progression, or low-dose S-1 (20 mg/m^2) plus oxaliplatin followed by second-line reduced-dose chemotherapy combined with S-1 and irinotecan at the time of progression. Bevacizumab was added as a first-line chemotherapy option. Reduced-dose combination therapy significantly prolonged the PFS compared with full-dose monotherapy (6.2 months ; 95% CI 5.3–8.3) with HR 0.72 (95% CI 0.52–0.99 ; p = 0.047) and reduced the incidence of grade 3–4 adverse events (62% in the monotherapy group vs. 43% ; p = 0.014) (graded using NCI-CTCAE, version 4.0). Although the doses of S-1 and irinotecan in this regimen were different from those in Japan, the findings are considered useful.

Regorafenib and FTD/TPI have both demonstrated significant prolongation of OS in phase III trials compared with placebo in patients with unresectable CRC who were refractory or intolerant to all previous therapies and have become standard agents in the last line setting because of their oral, mildly toxic, and well-tolerated characteristics (13).

Aparicio *et al*. conducted a multicenter phase II study to evaluate the efficacy of regorafenib in previously treated patients with unresectable CRC aged 70 years and older. The PFS was 2.2 months, while the OS was 7.5 months. Grade 3–4 treatment-related adverse events were observed in 83% of patients, with asthenia being the most frequent adverse event (graded using NCI-CTCAE, version 4.0). Discontinuation owing to toxicity was observed more frequently in patients aged 80 years and older and in those with an ECOG performance status ≥1 (14). Similarly, another phase II study in 47 elderly patients (median age, 80 years) in Spain evaluated the efficacy and safety of regorafenib as a first-line therapy (15). The median PFS and OS were 5.6 and 16 months, respectively, and 25% of the patients required dose reduction. Two patients developed grade 5 toxicity, and the incidence rates of grade 3–4 hypertension and asthenia were 32% and 30%, respectively (graded using NCI-CTCAE, version 4.0). These results suggest that regorafenib can be administered to previously treated elderly patients aged >70 years ; however, caution should be observed to avoid the occurrence of adverse effects. As a reduced dose of regorafenib has also been reported to be effective in elderly patients (16), an initial reduced dose for elderly patients should be established in the future.

FTD/TPI causes milder non-hematologic toxicity and may be better tolerated than regorafenib, suggesting that it may be more suitable for use in elderly patients (13). Although the effectiveness of adding bevacizumab to FTD/TPI for patients who are not suitable for potent therapy has already been reported (17), Oki *et al*. conducted a phase II study investigating the efficacy and

safety of FTD/TPI plus bevacizumab in elderly patients with unresectable colorectal cancer (18).

In this study, FTD/TPI plus bevacizumab was administered every 4 weeks to 39 patients with untreated unresectable colorectal cancer aged >70 years. The median PFS, median OS, ORR, and disease control rate were 9.4%, 22.22%, 40.5%, and 86.5%, respectively. The common grade 3–4 adverse events included neutropenia (71.8%), leukopenia (51.3%), anorexia (15.4%), febrile neutropenia (10.3%), and fatigue (10.3%)(graded using NCI-CTCAE, version 4.0), indicating that FTD/TPI plus bevacizumab is an effective and well-tolerated regimen for elderly patients.

A phase III study (SOLSTICE study) evaluating the superiority of FTD/TPI plus bevacizumab over capecitabine plus bevacizumab in patients who are not suitable for aggressive treatment has been conducted since 2019, and the results are still awaiting (19). By contrast, in clinical practice, irinotecan, oxaliplatin, continuous infusion 5-fluorouracil and leucovorin (FOLFOXIRI) plus bevacizumab, a triple therapy, can be considered as a first-line treatment for elderly patients in good physical condition and with well-preserved major organ function, especially in those with BRAFV600E mutation-positive or right-sided tumors. In fact, the triplet plus bevacizumab (TRIBE) and TRIBE2 trials, which included patients aged 70 years and older with an ECOG PS ≤2 and aged 71–75 years with an ECOG PS of 0, demonstrated the superiority of the triple-drug combination plus bevacizumab over the two-drug combination plus bevacizumab. Marmorino *et al*. conducted a pooled analysis of these trials to evaluate the efficacy and safety of triple-drug combination therapy in elderly patients (20). Among the 1,187 patients analyzed, 1,005 (85%) were aged <70 years, whereas 182 (15%) were aged 70–75 years.

The analysis showed no interaction between age and response rate, PFS benefit, or increased risk of grade 3–4 adverse events associated with intensified chemotherapy. However, grade 3–4 diarrhea occurred in 27% of patients, while febrile neutropenia occurred in 16% of patients aged 70–75 years who received FOLFOXIRI plus bevacizumab (graded using NCI-CTCAE, version 4.0), suggesting that initial dose reduction and possibly the use of granulocyte colony-stimulating factor (G-CSF) for primary prophylaxis may be necessary. In conclusion, FOLFOXIRI plus bevacizumab is a more effective option compared with the combination of two drugs plus bevacizumab regardless of age ; however, the tolerability of this regimen should be carefully evaluated in elderly patients and should be implemented with sufficient dose reduction and strict control.

4) TRENDS IN IMMUNOTHERAPY OF GI CANCER FOR ELDERLY PATIENTS

Recently, treatment with a combination of ICIs and chemotherapy has become the standard of care for many types of cancers, and promising results have been reported in phase III trials in patients with gastrointestinal cancer. However, to date, no clinical trials have investigated the efficacy and tolerability of ICI therapy in elderly patients with gastrointestinal cancers. The CheckMate 649 study is a global phase III trial, including Japan, that examined the superiority of nivolumab plus chemotherapy over standard chemotherapy, oxaliplatin, continuous infusion 5-fluorouracil plus leucovorin (FOLFOX)/capecitabine plus oxaliplatin (CAPOX) as the first-line treatment for unresectable advanced or recurrent gastric/esophagogastric junction/esophageal adenocarcinoma (21). The primary endpoints of the study were achieved, that is, nivolumab plus chemotherapy showed significant OS and PFS benefit compared with chemotherapy alone in the population with a combined positive score (CPS) ≥5. In the subgroup of elderly patients (≥65 years) with a CPS ≥5, the median OS times were 14.3 months for nivolumab plus chemotherapy and 11.2 months for chemotherapy alone (HR 0.72, 95% CI 0.57–0.92).

ATTRACTION-4 assessed the superiority of nivolumab plus chemotherapy (oxaliplatin and S-1 or capecitabine) over chemotherapy as a first-line treatment for unresectable advanced or recurrent gastric cancer and esophagogastric junction cancer in an Asian population (22). Although nivolumab plus chemotherapy did not demonstrate an OS benefit, a significant improvement was observed in the PFS. In this study, 368 patients aged 65 years and older were included, and the PFS and OS times were 8.9 and 17.9 months, respectively (HR for PFS 0.83, HR for OS 1.01).

KEYNOTE-590 is a global phase III trial evaluating the efficacy of pembrolizumab or placebo in combination with 5-FU/cisplatin chemotherapy in patients with previously untreated unresectable or progressively recurrent esophageal cancer, including adenocarcinoma of the esophagogastric junction (23). Pembrolizumab demonstrated a significant OS, PFS, and ORR benefit, regardless of the histology or programmed death ligand 1 (PD-L1) expression levels. A subgroup analysis of OS and PFS in patients aged <65 years or >65 years demonstrated no age-specific effect.

The decline of the immune system with aging has been reported in studies using various preclinical models, which may indicate that ICIs may be less effective in elderly patients (24). However, a meta-analysis conducted by Landre *et al*., which investigated the efficacy of ICIs in patients with advanced solid tumors, including gastric cancer, by age group showed that ICI treatment is effective in patients aged >75 years (25). However, the improvement in survival was mainly observed after the administration of first-line treatment but was not observed after the provision of a second-line treatment. At this point, it is difficult to predict how aging of the immune system will affect the efficacy of ICI therapy ; since cancer and anticancer drug therapy itself may alter the immune system, it may be difficult to determine the indications for treatment based simply on age.

CONCLUSION

Gastric and colorectal cancers are the two most common types of cancer in Japan, with more than half of these cases occurring in elderly individuals. However, there is still a high unmet medical need for the appropriate treatment of elderly patients because of their limited understanding. Research on appropriate treatment strategies is still ongoing, but more efforts should be made to improve the patient outcomes and QOL, including improved monitoring and diagnosis, use of supportive care, measurement and treatment of malnutrition, and support for patient caregivers.

In addition, it is important to study the physiological aging process, including changes in pharmacokinetics and immune responses, which will facilitate the development of effective treatments based on these findings. Furthermore, clinical trials should be conducted to optimize the dosage of currently available drugs, evaluate their therapeutic efficacy in elderly patients, and incorporate a comprehensive evaluation of the elderly.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

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