Chemotherapy and other drug therapies for older patients with cancer: JSMO-JSCO clinical practice guidelines

Gastrointestinal cancer

CQ 4

Can the concomitant administration of an oral fluoropyrimidine drug and cisplatin or oxaliplatin be recommended for geriatric patients with unresectable metastatic gastric cancer?

Recommendation

1. It is proposed that cisplatin not be administered to geriatric patients with HER2-negative unresectable metastatic gastric cancer. [Strength of recommendation: 2 (rate of agreement: 85%); strength of evidence: C]
2. It is proposed that oxaliplatin be concomitantly administered. [Strength of recommendation: 2 (rate of agreement: 69%); strength of evidence: C]

Background

1. Standard chemotherapy for unresectable metastatic gastric cancer

The SPIRITS study, which is a clinical study conducted in Japan, has shown that the combination therapy of S-1 + cisplatin significantly prolongs the survival of patients with unresectable metastatic gastric cancer compared with S-1 monotherapy. S-1 + cisplatin therapy has now been recognized as a standard therapy for this disease in Japan. However, this therapy requires a large infusion volume to prevent cisplatin-induced renal dysfunction. Therefore, most patients require hospitalization for cisplatin administration. Another issue to be addressed is that cisplatin can cause severe gastrointestinal adverse events, such as nausea and vomiting. A clinical study conducted overseas with the aim of examining whether it is possible to replace cisplatin with oxaliplatin reported that oxaliplatin-based therapy was shown to be non-inferior compared to cisplatin-based therapy. It was concluded that it is possible to replace cisplatin with oxaliplatin. Meanwhile, another clinical study conducted in Japan examined whether it is possible to replace cisplatin with oxaliplatin in combination therapy with S-1. This study showed that the non-inferiority of S-1 + oxaliplatin compared to S-1 + cisplatin could not be validated. However, it was found that the clinical effects of these therapies were almost equivalent to each other. Based on these results, it is a consensus in Japan that cisplatin can be

replaced with oxaliplatin even in combination with S-1.. Therefore, standard treatments for unresectable metastatic gastric cancer include S-1 + cisplatin therapy and S-1 + oxaliplatin therapy. Additionally, not only S-1 but also capecitabine is used in combination therapy with cisplatin or oxaliplatin.

2. Chemotherapy for geriatric patients with unresectable metastatic gastric cancer

Few large-scale clinical studies have been conducted on geriatric patients with unresectable metastatic gastric cancer. Sufficient data from the direct comparison of S-1 or capecitabine monotherapy and combination therapy with cisplatin or oxaliplatin are not available. Moreover, although the subjects of certain clinical studies include geriatric patients, there is a tendency for such studies to exclude geriatric patients with a comorbidity or reduced organ function. Therefore, geriatric patients in such studies may be different from the majority of geriatric patients in real-world settings.

Generally, in the clinical practice, the physician tends to select a treatment considering the condition of the geriatric patient. Combination therapy with cisplatin or oxaliplatin is administered only in patients in a favorable condition, and the monotherapy of S-1 or capecitabine is administered in other patients.

Given the above, the key clinical issue was identified: “What kind of chemotherapy is appropriate for gastric cancer in geriatric patients?” To address this issue and to examine the necessity of administering combination therapy with platinum-based drugs for unresectable metastatic gastric cancer, the following clinical question (CQ) was set: “Can the concomitant administration of an oral fluoropyrimidines and cisplatin or oxaliplatin be recommended for geriatric patients with unresectable metastatic gastric cancer?” Because not only S-1 but also capecitabine is used in treating such patients, the present CQ did not limit the drug to be S-1 and instead used the term “oral fluoropyrimidines.”

Literature review and clinical interpretation

Standard chemotherapies for recurrent metastatic gastric cancer include S-1 + cisplatin therapy and S-1 + oxaliplatin therapy. The 2018 version of Gastric Cancer Treatment Guidelines contains a conditional recommendation that chemotherapy be administered in geriatric patients with unresectable metastatic gastric cancer as long as the condition of the patient is carefully evaluated and as long as an appropriate regimen is selected. The recommendation did not provide clear details because the eligibility criteria of existing,

large-scale phase III studies have included subjects aged up to 75 years. Thus, patients geriatric than 75 years were not enrolled in such studies. Compared with combination therapy with cisplatin, S-1 monotherapy is more tolerable and simpler. Thus, it is relatively easy to introduce S-1 monotherapy to geriatric patients. Although high therapeutic effects can be expected from S-1 + cisplatin combination therapy, concerns about an increase in adverse events and an impact on renal function remain. Meanwhile, oxaliplatin has recently been used instead of cisplatin in an increasing number of cases. An advantage of oxaliplatin is that it can be administered to the patient on an outpatient basis. However, it can cause adverse events such as hematological toxicity and sensory peripheral neurotoxicity. Thus, we examined the necessity of concomitantly administering platinum-based drugs with S-1 in drug therapy for unresectable metastatic gastric cancer.

The following five outcomes were adopted for the present CQ: prolongation of OS, prolongation of progression-free survival (PFS), improvement in the complete response rate, incidence of adverse events of grade 3 or more, and maintaining quality of life. Furthermore, HER2-negative cases were anticipated in considering recommendations for the present CQ. Based on the discussion in the recommendation panel, recommendations were separately examined for concomitant administration of cisplatin and that of oxaliplatin. Moreover, based on opinions from external evaluation, the CQ was modified such that the CQ clearly indicates that the issue at hand is the combination therapy of an oral fluoropyrimidines and cisplatin or oxaliplatin.

The initial screening was conducted through a systematic literature search that extracted 37 papers. These were narrowed down to twelve in the second screening, during which retrospective studies in single facilities on a small number of cases and overviews of papers that do not include a subset analysis of geriatric patients were excluded.

Only two randomized comparative trials (RCTs) matched the CQ[1,2]. Only a small number of geriatric patients were enrolled in both studies. Also, other intervention studies were subset analyses. Therefore, it was determined that the strength of the body of evidence from intervention studies is “weak (C).” In a multicenter phase III study on 50 geriatric patients aged 70 years or geriatric, the following two groups were compared in terms of OS: a group of patients who received the capecitabine + oxaliplatin therapy and that of patients who received capecitabine monotherapy. OS in the two groups were 11.1 months and 6.3 months, respectively (hazard ratio [HR]: 0.58; 95% confidence interval

[CI]: 0.30-1.12; p = 0.108)[1]. Additionally, a randomized phase II study on frail or geriatric patients (median age of 75 years; range, 50-87 years) showed that OS in the oxaliplatin + capecitabine therapy group (19 subjects) was 9.5 months and in the capecitabine monotherapy group (19 subjects) was 3.6 months (HR not stated)[2]. Subset analyses of geriatric subjects (70 years or geriatric) were conducted in phase III studies in Japan (SPIRITS and G-SOX). In the SPIRITS study, the HR of S-1 + cisplatin therapy relative to S-1 monotherapy was 0.95 (95% CI: 0.71-1.27)[3], and in the G-SOX study, the HR of S-1 + oxaliplatin therapy relative to S-1 + cisplatin therapy was 0.857 (95% CI: 0.629-1.167)[4]. Results for PFS were similar to those of OS analyses. In the RCTs, PFS was 2.6-4.7 months for S-1 monotherapy, 5.6-7.1 months for oxaliplatin combination therapy[4], and 5.5-6.0 months for cisplatin combination therapy[3]. It was found that PFS tends to be longer when platinum-based drugs are concomitantly used. Results for response rate were also similar to those of OS and PFS. In the RCTs, the response rate was 11-31% for S-1 monotherapy, 42-53% for oxaliplatin-based therapy[4], and 43% for cisplatin-basedtherapy[3]. The response rate tends to be slightly higher when platinum-based therapies are concomitantly used. The incidence rate of adverse events of grade 3 and 4 tends to be higher for platinum-based therapies than for S-1 monotherapy. Particularly, there was an increase in hematological toxicity and gastrointestinal toxicity (nausea and decreased appetite)[3]. In the oxaliplatin-based therapy group in the G-SOX study, peripheral neurotoxicity of grade 3 or more were observed in approximately 5% of patients including non-geriatric patients[4]. Quality of life (QOL) was examined in only one RCT that compared the cisplatin + S-1 with oxaliplatin + S-1. Compared with the cisplatin combination therapy group, QOL evaluated through Functional Assessment of Cancer Therapy - General (FACT-G) was significantly higher in the oxaliplatin-based therapy group[5]. The above findings suggest that compared with fluoropyrimidine monotherapy, combination therapy with cisplatin or oxaliplatin may achieve a higher response rate and longer PFS in geriatric patients with unresectable metastatic gastric cancer. However, it has not been confirmed that such combination therapy can also prolong OS. Additionally, it should be noted that administering the combination therapy may lead to an increase in adverse events. Therefore, it was determined that it would be “mildly recommended” that cisplatin not be concomitantly administered. However, compared with cisplatin, adverse events caused by oxaliplatin are overall milder. It was determined that the benefit slightly exceeds the risk in oxaliplatin-based therapy for

geriatric patients who have favorable organ function and who do not have a serious comorbidity. Thus, it was decided that oxaliplatin combination therapy can be considered and that it would be “mildly recommended” that oxaliplatin be concomitantly administered.

Voting results

Following the confirmation of the above, one of the committee members withdrew from voting on the grounds of an academic conflict of interest as they were involved in the above-mentioned phase II study. Thirteen panel members participated in voting.

1. Cisplatin-based therapy: From among thirteen panel members, eleven voted for “mild recommendation for not administering the therapy” and two voted for “strong recommendation for not administering the therapy.” It was determined that the level of recommendation would be “mild recommendation (proposal) for not administering cisplatin-based therapy.” Also, two committee members who voted for “strong recommendation for not administering cisplatin-based therapy” explained the reasons for their decisions as follows: “an impression of the details discussed the above” and “concerns about severe adverse events in organs such as the kidneys.”
2. Oxaliplatin-based therapy: From among thirteen panel members, nine voted for “mild recommendation for administering the therapy” and four voted for “mild recommendation for not administering the therapy.” It was determined that the level of recommendation would be “mild recommendation (proposal) for administering the therapy.”

Future research questions

It is assumed that the balance between the expected effects and anticipated harms and burdens of chemotherapy in geriatric patients differs from that in non-geriatric patients. However, no studies that investigated such a balance were found through our literature search. A particular focus should be placed on this aspect when selecting a chemotherapy that can cause different adverse events. This balance is particularly important in choosing from several treatments with different adverse events. Such differences should be further investigated in future studies.

References

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CQ 5

Can administering postoperative adjuvant chemotherapy be recommended for geriatric patients aged 70 years or older who have undergone colon cancer surgery (R0 resection, stage III)? If yes, what kind of treatment would be recommended?

Recommendation

1. It is proposed that postoperative adjuvant chemotherapy be administered for geriatric patients aged 70 years or older who have undergone radical resection of stage III colon cancer. [Strength of recommendation: 2 (rate of agreement: 79%); strength of evidence: C]
2. It is proposed that oxaliplatin concomitant therapy not be administered if adjuvant chemotherapy is administered. [Strength of recommendation: 2 (rate of agreement: 71%); strength of evidence: C]

Background

1. Standard adjuvant chemotherapy for colon cancer following radical resection

Postoperative adjuvant therapy based on a fluoropyrimidines for radically resected stage III colon cancer can reduce the relapse rate and the mortality rate compared with surgery alone. Furthermore, the efficacy of fluoropyrimidines does not change depending on whether they are intravenously administered or orally administered. In western countries clinical studies have reported that postoperative adjuvant chemotherapy that adopted the combination therapy of a fluoropyrimidine and oxaliplatin reduced the risk of relapse and mortality by 20% and the relapse rate by 5%. However, adjuvant chemotherapy involving oxaliplatin-based therapy can cause dose-dependent peripheral sensory neurotoxicity, which have a significant impact on the patient's quality of life (QOL). A study has reported that grade 3 peripheral sensory neurotoxicity remained in approximately 13% of patients even 3 years following the completion of treatment. Such disorders affect the patient's everyday life.

2. Adjuvant chemotherapy for geriatric patients with radically resected colon cancer

Japanese and Western countries treatment guidelines recommend that treatment for patients with radically resected stage III colon cancer be provided by paying great attention to organ function and comorbidity and that geriatric patients aged 70 years or older not be excluded solely based on their age because preventive effects equivalent to

those in non-geriatric patients can be expected through treatment. Meanwhile, a clinical study has proven the efficacy of adjuvant chemotherapy involving oxaliplatin combination therapy. An integrated analysis of the study has shown that oxaliplatin combination therapy achieves limited efficacy in terms of disease-free survival (DFS) and overall survival because there are increased mortality risks in geriatric patients aged 70 years or older due to the onset of other cancers and diseases. Moreover, it has been reported that compared with non-geriatric patients, the completion rate of postoperative adjuvant chemotherapy is low in geriatric patients aged 70 years or older.

Given the above, the key clinical issue was identified: “What kind of drug therapy is appropriate for colon cancer in geriatric patients?” To address this issue, the following clinical question (CQ) was set: “Is it meaningful to administer postoperative adjuvant chemotherapy in geriatric patients aged 70 years or older who have undergone colon cancer surgery (R0 resection, stage III)? If yes, what kind of treatment would be recommended?”

Literature review and clinical interpretation

It has been recommended that postoperative adjuvant therapy based on a fluoropyrimidine be administered for radically resected, stage III colon cancer through combination therapy with oxaliplatin or capecitabine monotherapy. It has been recommended that such therapy be administered by paying attention to the organ function and comorbidity of the patient and by selecting appropriate patients and that geriatric patients aged 70 years or older not be excluded solely based on their age because preventive effects equivalent to those in non-geriatric patients can be expected in geriatric patients through such therapy. Meanwhile, an integrated analysis has indicated that the effects of adding oxaliplatin to treatment for geriatric patients aged 70 or older are limited in terms of DFS and overall survival (OS). Moreover, it has been reported that compared with non-geriatric patients, the implementation rate of postoperative adjuvant chemotherapy is low in geriatric patients aged 70 years or older[1]. Further, combination therapy with oxaliplatin can cause dose-dependent peripheral sensory neurotoxicity , which is a serious concern. Taking all this into account, we examined the significance of administering postoperative adjuvant chemotherapy in geriatric patients aged 70 years or older who have undergone surgery for stage III colon cancer. We also considered optimal regimens for such patients.

The following outcomes were adopted: prolongation of survival, prolongation of relapse-free survival, incidence of adverse events of grade 3 or more, and maintaining QOL. Of these outcomes, we referred to relapse-free survival as DFS while performing a literature review because clinical studies that were adopted in the literature review did so. CQ 5 was set as follows: "Is it meaningful to administer postoperative adjuvant chemotherapy in geriatric patients aged 70 years or older who have undergone colon cancer surgery (R0 resection, stage III)?" However, it was pointed out that the expression "Is it meaningful to administer...?" was not accurately reflecting the context. Thus, the expression was changed to "Can XXX be recommended?" It was determined that a recommendation for the relevant therapy would be considered first and that a recommendation for whether or not to add oxaliplatin would subsequently be determined. The initial screening was conducted through a systematic literature search, which extracted 60 papers, all of which were extracted in the second screening. To answer the present CQ, it is necessary to compare the following two groups: an intervention group consisting of geriatric patients aged 70 years or older (oral fluoropyrimidine monotherapy, 5-FU/LV) and a control group (chemotherapies such as FOLFOX and CapeOX, which include oxaliplatin). However, no studies that adopted such a design were found. Subset analyses of three randomized comparative trials (RCTs) (NSABP C-07[2], MOSAIC[3], and X-ACT[4]) and eight observational studies were relevant to the CQ. The following observational studies were excluded: phase II studies, clinical studies on a small number of subjects, and studies in which findings were adjusted using propensity scores. Additionally, those with high bias risks at the stage of creating an evaluation sheet were also excluded. In the final stage, eleven papers were adopted for evaluating the body of evidence. It was determined that the strength of the body of evidence of intervention studies was "weak (C)."

In a subset analysis of the NSABP C-07 study[2] of 396 patients aged 70 years or older who had undergone surgery for stage II or III colon cancer, adding oxaliplatin to 5-FU/LV did not improve the survival rate (hazard ratio [HR]: 1.18; 95% confidence interval [CI]: 0.86-1.62). 5-FU/LV is the combination therapy of a fluoropyrimidine and a folic acid analog. Further, in a subset analysis of the MOSAIC study[3] of 315 patients aged 70-75 years who had undergone surgery for stage III colon cancer, the usefulness of adding oxaliplatin was also not validated (HR: 0.98; 95% CI: 0.62-1.56). Moreover, in a subset analysis of the X-ACT study[4] of 396 geriatric patients aged 70 years or older, the non-

inferiority of capecitabine monotherapy to 5-FU/LV was examined. Results showed that the efficacy of the therapy was equivalent to that in non-geriatric patients (HR: 0.91; 95% CI: 0.65-1.26). Observational studies, even including a pool analysis of several databases and an integrated analysis of previously reported RCTs, indicate the usefulness of monotherapy with a fluoropyrimidine in postoperative adjuvant chemotherapy for geriatric patients aged 70 years or older. However, the usefulness of adding oxaliplatin was not validated[5]. Meanwhile, a recent integrated analysis of individual patient data obtained from the NSABP C-08, XELOXA, X-ACT, and AVANT studies showed that compared with 5-FU/LV, postoperative adjuvant chemotherapy with CapeOX or FOLFOX in patients aged 70 years or older improved DFS (HR: 0.77; 95% CI: 0.62-0.95; p = 0.014) and OS (HR: 0.78; 95% CI: 0.61-0.99; p = 0.045). However, the incidence rate of adverse events of grade 3 or more was higher in the oxaliplatin combination therapy group. Results for DFS were similar to those for OS. It was found that adjuvant chemotherapy in geriatric patients aged 70 years or older can prolong the relapse-free survival period. Few papers investigated adverse events. We found only one RCT and one observational study[6] that investigated them. In both studies, there was a tendency for adverse events to increase when oxaliplatin combination therapy was administered compared with fluoropyrimidine monotherapy. No papers that evaluated QOL were found in our literature search.

Given the above, it was considered that the usefulness of fluoropyrimidine monotherapy as a postoperative adjuvant chemotherapy in geriatric patients aged 70 years or older with stage III colon cancer is equivalent to that in non-geriatric patients. However, there is little evidence that indicates the usefulness of adding oxaliplatin. As such usefulness cannot be confirmed, the recommendation panel determined that an increase in adverse events is a more significant factor. At present, it is considered that postoperative adjuvant chemotherapy may be administered in geriatric patients with a favorable performance status (PS) and favorable organ function who do not have serious comorbidities.

Voting results

Following the confirmation of the above, fourteen panel members participated in voting.

1. Postoperative adjuvant chemotherapy: In the first round of voting, of fourteen panel

members, seven voted for “strong recommendation for administering the therapy” and seven voted for “mild recommendation for administering the therapy.” The level of recommendation could not be determined in this round. Voting was again conducted following a post-voting meeting. In this round, three voted for “strong recommendation for administering the therapy” and eleven voted for “mild recommendation for administering the therapy.” It was determined that the level of recommendation would be “mild recommendation (proposal) for administering the therapy.”

2. Adding oxaliplatin: From among fourteen panel members, two voted for “mild recommendation for adding oxaliplatin,” ten voted for “mild recommendation for not adding oxaliplatin,” and two voted for “strong recommendation for not adding oxaliplatin.” It was determined that the level of recommendation would be “mild recommendation (proposal) for not adding oxaliplatin.”

Two committee members who voted for “mild recommendation for adding oxaliplatin” subsequently suggested that it would be ideal to use oxaliplatin after carefully assessing the benefit-harm balance based on a thorough evaluation of the appropriateness of adding the drug. They also suggested that in doing so, PS, organ function, and the presence of serious comorbidities should be taken into account. Furthermore, other committee members suggested that, irrespective of whether or not oxaliplatin is concomitantly administered, intravenous infusion would be more appropriate than oral administration when administering a fluoropyrimidine because it is important to ensure medication adherence in geriatric cases.

Future research questions

Evaluable evidence is limited to that from a subgroup analysis of an RCT that includes geriatric subjects. Thus, it is necessary to conduct an RCT that directly investigates geriatric patients.

References

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CQ 6

Can the use of bevacizumab be recommended in the initial chemotherapy for geriatric patients with unresectable metastatic colorectal cancer?

Recommendation

It is proposed that bevacizumab be administered to geriatric patients with unresectable colorectal cancer in the initial chemotherapy. [Strength of recommendation: 2 (rate of agreement: 86%); strength of evidence: C]

Background

1. Standard drug therapy for unresectable metastatic colorectal cancer

The appropriate use of cytotoxic anticancer drugs and molecular targeted drugs in the initial chemotherapy has been found to significantly increased the 50% survival period by approximately 30 months in patients with unresectable metastatic colorectal cancer. The 50% survival period was 12 months when monotherapy with a fluoropyrimidine as adopted as a major therapy. Major drug therapies for unresectable metastatic colorectal cancer include fluoropyrimidine monotherapy, fluoropyrimidine + oxaliplatin combination therapy, fluoropyrimidine + irinotecan combination therapy, and fluoropyrimidine + oxaliplatin + irinotecan combination therapy. In addition to these, bevacizumab, an anti-vascular endothelial growth factor drug, is concomitantly administered. Alternatively, cetuximab or panitumumab, which are anti-epidermal growth factor receptor (EGFR) antibodies, are concomitantly administered for wild-type *RAS* types in cancer tissue. Bevacizumab, cetuximab, and panitumumab are molecular targeted drugs. If these drugs are inefficacious, regorafenib or trifluridine/tipiracil are administered. Administering such drugs as required can prolong the survival period. In general, compared with monotherapy, combination therapy is more efficacious and gives rise to more adverse events. When looking at combination therapies, as the number of drugs used in the therapy increases, both anti-tumor effects and the severity of adverse events increase. Therefore, the optimal therapy is selected from among the above options, taking into account the general condition of the patient, treatment goals, and the drug sensitivity of the cancer.

2. Drug therapy for unresectable metastatic colorectal cancer in geriatric patients

It has been suggested that in general, compared with non-geriatric patients, the risk of

adverse events such as fluoropyrimidine-induced hematological toxicity is higher in geriatric patients. It has also been suggested that oxaliplatin-induced peripheral sensory neurotoxicity have a significant impact on quality of life (QOL). Several clinical studies on geriatric subjects have suggested that combination therapy of a reduced dose of capecitabine, which is an oral fluoropyrimidine , and oxaliplatin in patients for whom standard therapies cannot be administered does not improve PFS. Meanwhile, an integrated analysis of clinical studies has shown that the efficacy and tolerability of fluoropyrimidine + oxaliplatin combination therapy (FOLFOX) in geriatric patients were similar to those in non-geriatric patients. In terms of molecular targeted drugs, the combination therapy of capecitabine and bevacizumab has been reported to improve PFS. However, the therapy increased the risk of grade 3 or more thrombus and embolism. Additionally, the effects of prolonging survival from the therapy are smaller in geriatric patients than in non-geriatric patients. There is also a tendency for the therapy to increase the incidence rate of adverse events and their level of severity. Thus, it has been considered that the benefit of the therapy is small relative to the risk. Therefore, QOL tends to be prioritized in selecting a treatment for a geriatric patient. Particularly, questions related to the use of bevacizumab in a geriatric patient are frequently raised in the clinic.

Given the above, the key clinical issue was identified: “What kind of drug therapy is appropriate for unresectable metastatic colorectal cancer in geriatric patients?” To address this issue, the following clinical question (CQ) was set: “Can the use of bevacizumab be recommended in the initial chemotherapy for geriatric patients with unresectable metastatic colorectal cancer?”

Literature review and clinical interpretation

Drug therapies for unresectable metastatic colorectal cancer include fluoropyrimidine monotherapy, fluoropyrimidine + oxaliplatin combination therapy, fluoropyrimidine + irinotecan combination therapy, and fluoropyrimidine + oxaliplatin + irinotecan combination therapy. In addition to these, bevacizumab is concomitantly administered. Alternatively, cetuximab or panitumumab, which are anti-EGFR antibodies, are concomitantly administered for wild-type *RAS* types in cancer tissue. Bevacizumab, cetuximab, and panitumumab are molecular targeted drugs. If these drugs are inefficacious, regorafenib or trifluridine/tipiracil are administered. Administering such

drugs as required can prolong the survival period. In general, compared with monotherapy, combination therapy is more efficacious and gives rise to more severe adverse events. When looking at combination therapies, as the number of drugs used in the therapy increases, both anti-tumor effects and the severity of adverse events increase. Therefore, the optimal therapy is selected from among the above options, considering the general condition of the patient, treatment goals, and the drug sensitivity of the cancer. Therefore, questions related to the use of bevacizumab in a geriatric patient are frequently raised in the clinic.

Given the above, the key clinical issue was identified: "What kind of drug therapy is appropriate for unresectable metastatic colorectal cancer in geriatric patients?" To address this issue, the following clinical question (CQ) was set: "Can the use of bevacizumab be recommended in the initial chemotherapy for geriatric patients with unresectable metastatic colorectal cancer?"

The appropriate use of cytotoxic anticancer drugs and molecular targeted drugs has been found to significantly improve the prognosis of patients with unresectable metastatic colorectal cancer. Meanwhile, it has been suggested that compared with non-geriatric patients, the risk of fluoropyrimidine-induced hematological toxicity increases in geriatric patients[1]. It has also been suggested that oxaliplatin-induced peripheral sensory neurotoxicity have a significant impact on QOL[2,3]. Several studies on geriatric subjects have suggested that the combination therapy of capecitabine and a reduced dose of oxaliplatin in patients for whom intensive therapies cannot be administered does not improve PFS[4]. Meanwhile, an integrated analysis of clinical studies has shown that the efficacy and tolerability of FOLFOX in geriatric patients were similar to those in non-geriatric patients. In terms of molecular targeted drugs, although the combination therapy of bevacizumab and capecitabine has improved PFS, the therapy increased the risk of grade 3 or more thrombus and embolism[6,7]. As QOL tends to be prioritized in selecting a treatment for a geriatric patient, we examined the usefulness of bevacizumab in the initial chemotherapy for geriatric patients with unresectable metastatic colorectal cancer.
The following outcomes were adopted: prolongation of survival, prolongation of PFS, incidence of adverse events of grade 3 or more, and maintaining QOL.

The initial screening was conducted through a systematic literature search, which extracted 79 papers, of which fifteen papers were extracted through a second screening. Nine papers were excluded when an evaluation sheet was created. At the final stage, six

papers were adopted.

In order to answer the present CQ, it is necessary to compare the following two groups: a group consisting of geriatric patients who receive chemotherapy involving bevacizumab combination therapy (intervention group) and a group consisting of geriatric patients who undergo chemotherapy that does not involve bevacizumab combination therapy (control group). Such a design was employed in only one randomized comparative trial (RCT)[6]. A total of three observational studies were adopted. Two of these are prospective, cohort studies that compared a group of geriatric patients who received chemotherapy that involved bevacizumab combination therapy and a group of geriatric patients who received chemotherapy that did not involve bevacizumab combination therapy (control group)[7,8]. The remaining observational study is an integrated analysis of an RCT. At the final stage, the body of evidence was created based on six papers, including these three observational studies. The RCT[6] that matched the CQ is an open-label study that investigated patients aged 70 years or older with colorectal cancer. It is a relatively large-scale clinical study in which 280 subjects were enrolled. There were no particular factors to note that could undermine the evidence. It was determined that the strength of the body of evidence from intervention studies was “weak” because only one RCT was found.

In terms of OS, the AVEX study, which is the only RCT found, observed no significant difference between the group of subjects who received bevacizumab combination therapy through chemotherapy (140 subjects) and the group of subjects who received capecitabine monotherapy (140 subjects) (OS in the former group was 20.7 months and that in the latter group was 16.8 months; hazard ratio [HR]: 0.79; 95% confidence interval [CI]: 0.57-1.09; $p = 0.182$). Meanwhile, in terms of PFS, which was the primary endpoint of this study, significant prolongation was observed in the bevacizumab combination therapy group compared with the capecitabine monotherapy group (PFS in the former group was 9.1 months and that in the latter group was 5.1 months; HR: 0.53; 95% CI: 0.41-0.69; $p < 0.001$). There was a tendency for a higher incidence of adverse events of grade 3 or more in the bevacizumab combination therapy group than that in the capecitabine monotherapy group (40% vs. 22%). The incidence rates of serious adverse events were 14% and 8%, respectively. Bleeding of any grade was observed in 34 cases in the bevacizumab combination therapy group (25%) and in nine cases (7%) in the capecitabine monotherapy group. Other major adverse events of grade 3 or more that were observed in the bevacizumab combination therapy group and

the capecitabine monotherapy group were palmar-plantar erythrodysesthesia (16% vs. 7%), diarrhea (7% vs. 7%), and venous thrombosis (8% vs. 4%). Treatment-related death was observed in five cases in the bevacizumab combination therapy group and in four cases in the capecitabine monotherapy group. An increase in bleeding and thrombus events as well as palmar-plantar erythrodysesthesia was observed in the bevacizumab combination therapy group. In evaluating evidence, particular attention was paid to three integrated analyses, which are observational studies, for the following reasons: first, duplicate studies were adopted; second, secondary therapies were involved; and third, adverse events that were observed only in primary therapy were not clear. Findings on OS were not consistent between studies. Integrated analyses of two studies on primary therapy reported that significant improvement was observed in patients aged 65 years or older[9,10], whereas another analysis reported that no such improvement was observed[11]. Significant prolongation of PFS was observed in the bevacizumab combination therapy group in all of the analyses[9-11]. In terms of adverse events, a cohort study on approximately 6,800 Americans aged 65 years or older[7] found that combination therapy with bevacizumab is associated with an increased risk of arterial thromboembolism (HR: 1.82; 95% CI: 1.20-2.76). Meanwhile, no relationship between the therapy and cardiac death, cardiomyopathy, or congestive heart failure was observed in this study. Another study analyzed Australian subjects[8] divided into the following age cohorts: 65-74, 75-84, and 85 years or older. An increase in age-related adverse events of grade 3 or more was not observed in this study. The study concluded that age has no impact on bevacizumab-associated adverse events. It should be noted that only overseas studies were adopted for our examination, none of which included Japanese subjects. The evaluation of adverse events is overall consistent among studies. However, endpoints and study methods varied. No papers that evaluated QOL were found in our literature search.

The body of evidence from the RCT was prioritized in relation to the following outcomes: OS prolongation and PFS prolongation. It was determined that the effects of adding bevacizumab to capecitabine in geriatric patients aged 70 years or older does not significantly prolong OS but does significantly prolong PFS. However, the CQ is focused on geriatric patients, and there was only one study that matched the CQ. A conclusion cannot be drawn from existing studies as to the possibility of the prolongation of OS and PFS when bevacizumab is concomitantly administered with anticancer drugs other than capecitabine. This should be determined after results from currently ongoing clinical

studies are published. As the body of evidence from the RCT was also prioritized for adverse events, it was considered that bevacizumab combination therapy tends to increase the incidence of grade 3 or more adverse events. In determining the level of recommendation, the advantage (PFS prolongation) and the disadvantage (increased adverse events) of adding bevacizumab were discussed. It was considered that the advantage of adding bevacizumab exceeds the disadvantage from the perspective of patients' QOL for the following reasons: bevacizumab-induced adverse events, such as proteinuria and hypertension, can be managed relatively easily; the quality of such adverse events, namely, the degree of harm to the patient, is not necessarily significant; and the prolongation of PFS means that the general condition of the patient is stable during such a period, even if there is no significant OS prolongation.

Voting results

Following the above discussion, fourteen panel members participated in the first round of voting. From among these, one voted for "strong recommendation for using bevacizumab," nine voted for "mild recommendation for using bevacizumab," and four voted for "mild recommendation for not using bevacizumab." A recommendation could not be determined in this round. Voting was again conducted following a post-voting meeting. In this round, twelve voted for "mild recommendation for using bevacizumab" and two voted for "mild recommendation for not using bevacizumab." It was determined that the recommendation would be "mild recommendation (proposal) for using bevacizumab."

Future research questions

It is considered that the onset of grade 3 or more embolism has a significant impact on the patient's QOL, although the risk of such onset is low. Thus, it was considered that an important research issue to be addressed going forward would be selecting patients in accordance with the risk of embolism. Furthermore, the present CQ is limited to the use of bevacizumab. Therefore, it is necessary to perform similar investigations into other antibody agents with antiangiogenic effects as well as anti-EGFR agents.

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