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

Geriatric assessment

CQ 1

Can conducting a geriatric assessment for a geriatric cancer patient be recommended as a method of determining the appropriateness of cancer pharmacotherapy?

Recommendation

It is proposed that a geriatric assessment for a geriatric cancer patient be conducted as a method of determining the appropriateness of cancer pharmacotherapy. [Strength of recommendation: 2 (rate of agreement: 86%); strength of evidence: C]

Background

1. The characteristics of geriatric patients with cancer

Geriatric patients have diverse backgrounds that differ from those of non-geriatric patients. Characteristics of geriatric patients include decreased organ and physical functions due to physiological change, multiple diseases, polypharmacy multiple medications, and reduced social function. In treating geriatric patients, it is first necessary to understand these risks and then to propose a treatment method based on an understanding of such risks. Thus, it cannot always be determined whether or not a drug therapy is appropriate for certain geriatric patients based only on criteria such as organ function and performance status (PS).

2. Geriatric assessment

Geriatric assessment (GA) has been widely adopted in geriatric medicine. GA involves the measurement of physical functions (activities of daily living [ADL] and instrumental ADL [IADL]), cognitive function, social factors, family environment, and other related factors in accordance with certain established evaluation techniques as well as disease evaluation. GA has already been widely accepted as an established basic approach to the evaluation and treatment of general geriatric patients in the field of geriatric medicine. In cancer treatment, GA has been used as an index for predicting treatment toxicity and a decrease in quality of life (QOL) during treatment. It has also been used as a guideline for determining treatment plans, including the provision of supportive treatment to clearly

defined targets and the examination of the possibility of prolonging survival. Although conducting GA creates a burden in terms of time and human resources, the International Society of Geriatric Oncology (SIOG) recommends that GA be conducted.

Meanwhile, it is ideal to incorporate both geriatric and oncological concepts in treatment for geriatric patients with cancer because factors specific to clinical oncology can be observed in such patients, including a sudden deterioration in general condition and the prolonged impact of treatment.

3. General application of standard treatment to geriatric patients

Generally, a standard treatment is established through long-term development by establishing endpoints with a focus on prolonging survival as a treatment outcome. In this way, evidence is accumulated. It may be necessary to set more appropriate treatment goals for a geriatric patient compared with a non-geriatric patient. Such goals can include maintaining everyday life without affecting physical and cognitive functions, and maintaining QOL, in addition to prolonging survival. It is not always easy to apply a general, standard treatment to a geriatric patient even if it has been widely adopted for non-geriatric patients. Additionally, administering oral anticancer drugs to a geriatric patient who has impaired cognitive function or difficulty in managing medication may exacerbate their symptoms because it may not be possible to make an appropriate or prompt initial response in case of an adverse drug reaction. Great care needs to be taken so that anticancer drugs will not be administered to geriatric patients without due consideration. Such drugs should not be administered simply because they can be easily administered. The background of the patient should be understood in detail.

4. The current situation in Japan

In Japan, treatment plans for patients with cancer have been increasingly discussed in cancer boards and conferences involving professionals from various fields. That said, special considerations are not always made for geriatric patients or for physically, psychologically, or socially vulnerable patients. It is assumed that treatment methods are evaluated considering the treatment's benefit-risk balance. Ideally, GA would also be widely adopted in cancer consultation and treatment in Japan. GA has been widely adopted in geriatric medicine.

Given the above, the key clinical issue was identified: "For what kind of geriatric

patients is cancer pharmacotherapy appropriate?" To address this important issue, the following clinical question (CQ) was set: "Can conducting a geriatric assessment for a geriatric patient with cancer be recommended as a method of determining the appropriateness of cancer pharmacotherapy?"

Literature review and clinical interpretation

In the area of geriatric medicine, evidence has been established that appropriate intervention by a multidisciplinary team can improve prognosis. This can be achieved by identifying issues through multifaceted evaluation in GA[1]. Additionally, the International Society of Geriatric Oncology (SIOG) guidelines recommend that GA also be conducted in the field of oncology because GA is considered useful in detecting issues that have not been found by routine oncology care, determining treatment plans, and predicting prognosis and adverse events[2,3]. Thus, we examined whether or not it is useful to use GA in determining treatment plans for geriatric patients with cancer aged 65 years or older, for whom cancer pharmacotherapy has been considered, in terms of prolonging overall survival (OS) and reducing adverse events. We compared GA-based decisions with those made by the physician based on the patient's age and PS. The following factors were adopted as outcomes for the present CQ: OS prolongation, occurrence of a grade 3 or more adverse event, improvement of QOL, and completion of scheduled treatment. These outcomes reflect direct benefits or harms to patients.

To answer this CQ, a comparison between the following two groups should be made: a group for which treatment plans were determined through GA (intervention group) and a group for which treatment plans were determined based on the decisions of the physician (control group). However, such a design was employed in only one randomized control trial (RCT)[4] and one observational study[5]. Therefore, we also adopted a paper of an observational study that examined the prediction of prognosis (OS, the completion of scheduled treatment, and the prediction of adverse events) through GA for a cohort (single cohort) for which treatment regimens were determined based on decisions made by the physician. Additionally, early death and functional decline were evaluated as adverse events because they are generally evaluated as key outcomes in geriatric oncology research.

Only one RCT[4] matched the CQ. This study was a phase III study that validated the superiority of GA-based treatment regimens in terms of the treatment failure-free survival

period compared with a standard regimen based on age and PS. From among 449 patients aged 70 years or older with non-small-cell lung cancer, 251 were in the standard regimen group and 243 were in the GA-based treatment regimen group. In the standard therapy group (control group), carboplatin + pemetrexed was administered to patients aged 75 years or younger with PS 0-1 who had non-squamous cell carcinoma whereas carboplatin + gemcitabine was administered to patients aged 75 years or younger with PS 0-1 who had squamous cell carcinoma. In the same group, docetaxel monotherapy was administered in patients aged 76 years or older and/or with PS 2. In the study treatment group, patients were stratified into 3 predefined categories, namely fit, vulnerable, and frail, based on PS, ADL, IADL, Mini-Mental State Examination (MMSE), geriatric syndrome, comorbidities, and depression scores. Those with non-squamous cell carcinoma who were fit were assigned to the carboplatin + pemetrexed group; those with squamous cell carcinoma who were fit were assigned to the carboplatin + gemcitabine group; those who were vulnerable were assigned to the docetaxel monotherapy group; and those who were frail were assigned to best supportive care group. Results showed that no significant difference in OS was observed between the GA and control groups (6.4 months vs. 6.1 months; hazard ratio: 0.92; 95% confidence interval [CI]: 0.79-1.1). The incidence rate of adverse events of any grade was significantly lower in the GA group than in the control group (85.6% vs. 93.4%; p = 0.015). However, no significant difference was observed in the incidence rate of serious adverse events of grade 3 or more, which was adopted as an outcome for the present CQ (71.3% vs. 67.9%, p = 0.41).

Only one observational study was found that compared a GA group with a control group (a group for which treatment plans were determined based on the decision by the physicians in charge)[5]. Subjects in this study were aged 70 years or older with any type of cancer. A group of 70 subjects for whom treatment regimens were determined by the physicians was compared with a group of 65 subjects for whom treatment regimens were selected through GA. Primary endpoints were grade 3 or more adverse events and the completion rate of scheduled treatment. Further, it is noteworthy that intervention was performed following GA in this study. On average, 6.2 ± 2.6 interventions were performed following GA for 70.7% of subjects for whom GA was conducted. Results showed that performing interventions following GA significantly increased the completion rate of scheduled treatment (odds ratio: 4.14; 95% CI: 1.50-11.42), and there was a tendency for the incidence rates of adverse events to decrease (odds ratio: 0.69;

95% CI: 0.35-1.37).

All other observational studies evaluated a single cohort for which treatment regimens were determined by the physician. These studies examined whether the domains of pretreatment GA can be predictive factors for OS, the completion rate of scheduled treatment, and grade 3 or more adverse events. Three studies examining OS[6-8] found that nutrition and physical function[6], mental status and nutrition[8], social support, physical function, comorbidities, and mental status [7] were useful in predicting OS. Additionally, two studies[6,9] examining the completion rate of scheduled treatment found that nutrition[6], comorbidities, and IADL[9] were useful in predicting the completion rate of scheduled treatment. Lastly, seven studies[9-15] examining the prediction of adverse events found that comorbidities and IADL[9], IADL (for hematological toxicity) and MMSE (for non-hematological toxicity)[10], mental status and IADL[11], physical function (IADL, ADL, and falls) and social activity[12,13], nutrition and IADL[14], and nutrition and physical function[15] were useful in predicting adverse events. Given the above, it was considered that among these GA domains, evaluating physical function (ADL and IADL), nutritional status, and comorbidities would be useful.

The body of evidence from the RCT[4] is primarily considered in evaluating OS prolongation and a decrease in grade 3 or more adverse events from outcomes evaluated through a systematic review. Thus, it can be concluded that there is no significant difference in OS and adverse events of grade 3 or above between determining treatment plans through GA and determining those based on the decisions made by the physicians (based on age and PS). However, the usefulness of GA in this RCT needs to be carefully interpreted because, first, post-GA interventions were not performed in accordance with certain criteria and at the discretion of the physicians; second, the study only evaluated the treatment strategy defined for the study rather than the usefulness of GA itself; and third, issues with the study design have been noted, such as the appropriateness of criteria for fit, vulnerable, and frail groups. In other words, it is not possible to conclude that GA is not useful based solely on the results of this study. This study does not provide an answer to whether or not appropriate interventions for issues identified through GA can prolong OS. Additionally, it should be noted that the incidence rate of adverse events of any grade decreased in the group to which GA was applied in this study. In other words, the incidence rate of adverse events of grade 1 or 2 was lower in the GA group. The impact of these non-severe adverse events on geriatric patients was not examined.

Moreover, the body of evidence from observational studies indicates that certain domains such as physical function, nutrition, and comorbidities are useful in predicting prognosis and adverse events. Given the fact that GA-based, adverse event prediction scores, such as CARG score[12,13] and CRASH score[10], have already been used in daily oncology practice mainly in the United States and Europe, it is considered that a "mild recommendation" may be suitable for the present CQ.

No RCT was found that investigated the completion rate of scheduled treatment. Decisions for this outcome are made based on the body of evidence from observational studies (weak). It can be considered that GA is useful in predicting the completion rate of scheduled treatment. It can also be considered that intervention following GA can significantly increase the completion rate of scheduled treatment compared with a group of patients for whom treatment regimens are determined based on the decisions by the physicians (non-intervention group). No studies on the improvement of QOL were found in our literature search.

Furthermore, no consensus has been made as to which GA evaluation tool should be used.

Voting results

From among fourteen panel members, twelve voted for "mild recommendation for conducting GA," and two voted for "mild recommendation for not conducting GA." It was determined that the level of recommendation would be "mild recommendation (proposal) for conducting GA."

Future research questions

Interventions for issues identified through GA are not mentioned in the present CQ. Furthermore, only one observational study by Kalsi et al.[5] has defined post-GA intervention. Therefore, further studies are required that investigate whether it is possible to improve direct patient outcomes (OS prolongation and reduction of adverse events) through appropriate interventions for issues identified during GA. Further, there is still room for discussion as to whether the prolongation of survival is the most appropriate index for outcomes that indicate direct benefits and harms to geriatric patients with cancer. Further investigations into values held by older people are required, such as conducting a questionnaire survey of older people as to whether or not they prioritize QOL

improvement and maintaining physical and cognitive function other than OS prolongation.

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