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

Lymphoma

CQ 2

Is geriatric assessment useful in determining treatment plans for geriatric patients with diffuse large B-cell lymphoma?

Recommendation

It is proposed that geriatric assessment not be used in determining treatment plans for geriatric patients with diffuse large B-cell lymphoma. [Strength of recommendation: 2 (rate of agreement: 71%); strength of evidence: D]

* Geriatric assessment (GA) is useful in identifying issues that have been overlooked. The recommendation for CQ 2 does not rule out the use of GA in geriatric patients with cancer.

Background

1. Various types of malignant lymphoma

Lymphoma refers to lymphocytic malignant tumor. It is broadly categorized into B-cell lymphoma, T-cell lymphoma, and Hodgkin's lymphoma. According to the 2017 version of World Health Organization (WHO) classification, there are approximately 100 types of lymphoma. Standard treatment is not available for every type of lymphoma. Treatment methods vary depending on the disease type, including molecular targeted drugs. Lymphoma can be described as an aggregate of rare cancers. Furthermore, in many cases, depending on the speed of tumor growth, lymphoma is categorized into indolent lymphoma and aggressive lymphoma. Although it is difficult for indolent lymphoma to be cured through normal anticancer drug therapy, treatment of aggressive lymphoma aims to cure in many cases.

In Japan, approximately 30,000 people develop lymphoma annually. As the number of patients experiencing each disease type is small, it is often difficult to perform a large-scale comparative study. Therefore, high-quality clinical studies are limited to those on certain types of lymphoma. The incidence rate of diffuse large B-cell lymphoma (DLBCL) is the highest among all types of lymphoma. It is a major, aggressive lymphoma and highly sensitive to anticancer drugs. Curing DLBCL is possible through the completion of advanced anticancer therapy. The standard treatment for DLBCL is the

concomitant therapy of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP therapy). Rituximab is an anti-CD20 monoclonal antibody.

2. DLBCL prognosis prediction model

The median age of onset of lymphoma is 70 years. The majority of patients are older. Meanwhile, DLBCL treatment outcomes in geriatric patients are poor. One of the factors contributing to this is the fact that the intensity of treatment for such patients is frequently reduced to avoid serious treatment-associated toxicity. The physical and organ function of a geriatric patient is reduced as they grow older; therefore, drug therapy for a geriatric patient should not be the same as that for young patients. It is unlikely that administering a unified treatment in geriatric patients with DLBCL will achieve favorable treatment outcomes. Thus, it is necessary to select an appropriate treatment considering the condition of each individual patient. The international prognostic index (IPI) has been widely adopted as a prognosis prediction model for patients with DLBCL. In the IPI, the following aspects are considered: age (61 years or older), performance status (PS), lactate dehydrogenase level, extra-nodal disease, and disease period. However, treatment details are not modified based on the prognosis prediction through the IPI. The cellular origin of DLBCL as well as MYC and BCL-2 expression are known as factors for predicting a poor prognosis.

Meanwhile, there has been an increasing interest in geriatric assessment (GA) as a method of evaluating the physical, psychological, and social function of individual patients. More appropriate treatment methods can be selected if it is possible to predict treatment outcomes and the risks of adverse events based on individual GA results prior to the commencement of treatment. This can lead to the improvement of treatment outcomes.

Given the above, the key clinical issue was identified: “What kind of drug therapy is appropriate for malignant lymphoma in geriatric patients?” To address this issue, the following clinical question (CQ) was set and examined: “Is geriatric assessment useful in determining treatment plans for geriatric patients with diffuse large B-cell lymphoma?”

Literature review and clinical interpretation

Malignant lymphoma (hereafter referred to as simply lymphoma) is an aggregation of multiple diseases. According to the international WHO classification, it can be divided

into approximately 100 types. Each type has unique clinical and pathological characteristics. Therefore, possible treatment plans and prognoses vary among different types of lymphoma[1]. The number of patients with lymphoma has been increasing both within and outside Japan[2]. In 2014, the annual number of patients newly diagnosed with any type of lymphoma in Japan was slightly less than 30,000[3]. Of these patients, over 30% have DLBCL. DLBCL is a major disease type, and a large proportion of such patients are aged 65 years or older[4].

Treatment for DLBCL is administered with the aim of cure when possible. The standard treatment involves six to eight courses of the concomitant therapy of rituximab and CHOP therapy. The 5-year overall survival rate (OS) is 50-60%. The complete response rate and the 5-year OS decrease as the age of patients increases[5]. The IPI has been adopted in the clinic as a prognosis prediction model. Although age is one of the prognostic factors[6], treatment methods are currently not modified according to the prognosis prediction model.

Thus, we examined whether GA, which has been adopted in the field of geriatric medicine, is useful in predicting the prognosis of a geriatric patient with DLBCL and to determine if it is possible to administer the standard treatment in such patients. The following items were adopted for the outcomes of the present CQ: OS, progression-free survival (PFS), complete response rate, and the incidence of grade 3 or more adverse events.

CQ 2 was initially defined as follows: “Is geriatric assessment useful in predicting the prognosis of geriatric patients with diffuse large B-cell lymphoma?” The purpose of predicting prognosis for the CQ is to determine whether it is possible to select a standard treatment. Thus, based on opinions given through external evaluation, the wording was changed as follows: “Is geriatric assessment useful in determining treatment plans for geriatric patients with diffuse large B-cell lymphoma?”

A literature search was conducted with the following keywords: lymphoma, large B-cell, diffuse, geriatric assessment, and aged. Thirteen papers identified through the initial screening were narrowed down to seven through the second screening. No prospective, randomized comparative study was found. Two retrospective studies in Japan and five prospective, cohort studies in the United States and Europe were found. An evaluation sheet was created based on these seven papers[7-13]. The ages of subjects in these studies were 60 years or older in one paper, 65 years or older in four papers, and 70 years or older

in two papers. Subjects in all seven papers had comorbidities. A number of these papers involved cases of PS 2 or greater. Patient backgrounds varied significantly. Moreover, the details of treatment also varied. Certain papers included patients in whom rituximab was not administered, although it is a key drug in the standard treatment. Based on study methods and the background factors of subjects, bias was determined as -2 in all studies and the level of indirectness ranged from -2 to -1.

To answer the present CQ, it is necessary to compare two groups, namely one with favorable GA results and the other with poor GA results. However, comparisons in the retrospective studies were conducted after the patients' doctors determined treatment plans. Even though comparisons were made between two such groups in the prospective studies, decisions on treatment were at the discretion of the patients' doctors. Thus, it was difficult to answer the CQ based only on such observational studies. Additionally, few papers describe the following items, which have been adopted as outcomes: OS, PFS, complete response rate, and incidence of adverse events. Therefore, it was difficult to evaluate the papers as the body of evidence.

OS is discussed in all the papers. In certain papers, subjects were divided into two groups, namely a fit group and a non-fit group, and they were compared with each other. In other papers, subjects were divided into a fit group consisting of those who can undergo a standard treatment, an unfit group consisting of those who are unlikely to be able to undergo a standard treatment, and a frail group consisting of those for whom it was considered that best supportive care would be appropriate. Another paper compared groups by GA but failed to provide clear descriptions of the treatment regimens; therefore, the impact of treatment was not clear. A cohort study by a group of Italian researchers involved a large number of subjects (173 subjects) with clear descriptions of treatment methods[9]. In this paper, treatment outcomes equivalent to those of young patients were achieved in the fit group through a standard treatment, whereas treatment outcomes of the unfit group were poor (2-year OS: 84% in the fit group, 63% in the unfit group, and 40% in the frail group). In other papers, there was a tendency for OS to be favorable in the fit group, supporting the results of the Italian study.

Few high-quality, large-scale clinical studies have been conducted on lymphoma. However, it was suggested that, overall, weak evidence is available that indicates the usefulness of GA-based prognosis prediction. A consensus was achieved that GA may be useful in understanding the conditions of patients and that no strong evidence is available,

confirming that it is possible to determine the appropriateness of a standard treatment based on the results of GA. Meanwhile, it is necessary to ensure that patients who did not achieve favorable GA results will not experience disadvantages, such as being excluded from standard treatment, that otherwise would have led to favorable treatment outcomes. Thus, it was agreed to mildly recommend that GA not be used for the purpose of determining treatment plans. It is proposed in CQ 1 to conduct GA as a method of determining the appropriateness of cancer pharmacotherapy. It may appear that the recommendation in CQ 2 contradicts that in CQ 1. However, GA is useful in identifying issues that have been overlooked. The recommendation for CQ 2 does not rule out the use of GA in geriatric patients with cancer.

Voting results

From fourteen panel members, four voted for "mild recommendation for conducting GA," eight voted for "mild recommendation for not conducting GA," and two voted for "strong recommendation for not conducting GA." A discussion was held following voting. Two committee members who voted for "strong recommendation for not conducting GA" agreed with the proposal of "mild recommendation for not conducting GA." A consensus was achieved on the option of "mild recommendation for not conducting GA." Thus, it was determined to mildly recommend (propose) that GA not be conducted.

After the recommendation was decided, it was confirmed that conducting GA for the purpose of determining treatment plans may be recommended in the future if new research findings indicate so.

Future research questions

It is possible to aim for cure in DLBCL cases. Treatment effects equivalent to those in young patients can be achieved in geriatric patients if it is possible to administer a standard treatment. However, a standard treatment may impose an excessive burden on a geriatric patient. In such a case, the patient may experience disadvantages due to an increase in adverse events. Currently, it has been suggested that treatment methods can be stratified based on the evaluation of patients' conditions through GA. Although certain overseas guidelines recommend such an approach[14], sufficient evidence has not been provided. It is necessary to develop a model that considers GA and that can stratify treatment methods based on whether or not the patient can receive standard treatment. It

would be ideal if future studies involve the creation and validation of a model that comprehensively covers the prediction of the severity of neutropenia as well as the evaluation of cardiac function.

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CQ 3

Can drug therapies that include anthracyclines be recommended for geriatric patients aged 80 years or older with diffuse large B-cell lymphoma?

Recommendation

It is proposed that drug therapies that include anthracyclines be administered as long as great care is taken in selecting the treatment method. [Strength of recommendation: 2 (rate of agreement: 79%); strength of evidence: D]

Background

1. R-CHOP therapy: A standard treatment for diffuse large B-cell lymphoma

Malignant lymphoma is an aggregation of multiple diseases. Diffuse large B-cell lymphoma (DLBCL) is a major, aggressive B-cell lymphoma. Among all patients with any type of lymphoma, the highest number of patients have this type of lymphoma. High-quality, large-scale comparative studies have been conducted on DLBCL. The disease is one of the few types of lymphoma for which a standard treatment has been developed. A standard drug therapy for DLBCL involves the combination of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP therapy). Rituximab is a chimeric monoclonal antibody that targets CD20 in B-cells. CHOP therapy is the standard therapy for aggressive lymphoma. It is expected that this treatment method can cure approximately half of the patients.

2. Key drugs in R-CHOP therapy

Doxorubicin, an anthracycline drug, is a key drug in the treatment for DLBCL. One of the major adverse events that can be caused by this drug in clinical settings is cardiac toxicity. The drug cannot always be used in geriatric patients because many of them have cardiac diseases, such as heart failure, ischemic heart disease, and arrhythmia, as comorbidities. Additionally, the likelihood that doxorubicin causes nausea, vomiting, hypocytosis, and oral mucosal disease is high. In principle, it is possible to cure DLBCL through anticancer drug therapy. In doing so, it is necessary to maintain the intensity of treatment. Indeed, it is ideal that the standard treatment is administered to a geriatric patient as long as it is possible for them to tolerate the treatment. However, reports and opinions suggest that geriatric patients, particularly those aged 80 years or older, are unfit for the standard treatment. This is because, while it is possible to cure the disease in a

geriatric patient aged 80 years or older through R-CHOP therapy that includes doxorubicin, the incidence rate of severe adverse events, including treatment-related death, can increase.

Given the above information, the key clinical issue was identified: “What kind of drug therapies are appropriate for malignant lymphoma in geriatric patients?” To address this issue, the following clinical question (CQ) was set, with the aim of examining the significance of administering a drug therapy that includes doxorubicin in geriatric patients with DLBCL aged 80 years or older: “Can a drug therapy with doxorubicin be recommended for geriatric patients aged 80 years or older with diffuse large B-cell lymphoma?”

Literature review and clinical interpretation

The median age of the onset of DLBCL in Japan is over 70 years[1]. There has been an increase in the number of patients aged 80 years or older who are newly diagnosed with the disease. A standard treatment for untreated DLBCL is the combination R-CHOP therapy. A 5-year overall survival (OS) rate of 60% can be achieved in DLBCL through R-CHOP therapy. However, because R-CHOP therapy is a multiple combination therapy that includes the anthracycline drug doxorubicin, the therapy can cause adverse events such as hematological toxicity and cardiac toxicity. Particularly, the incidence rate of serious adverse events generally increases among geriatric patients aged 80 years or older. Meanwhile, it is possible to aim for the cure of DLBCL through drug therapy. Thus, it is important to avoid undertreatment, which can be caused by unnecessary dose reduction and medication omissions. In other words, the optimal treatment and the optimal dose of anticancer drugs that aim for long-term survival have not been determined for geriatric patients with DLBCL, including those aged 80 years or older. Given this situation, we examined the significance of administering drug therapies that include anthracycline drugs in geriatric patients with DLBCL aged 80 years or older.

Outcomes selected for the present CQ were OS, progression-free survival (PFS), complete response rate, the incidence rate of any adverse events, the incidence rate of cardiac toxicity, and the rate of treatment-related death.

CQ 3 was initially defined as follows: “Can drug therapies that include doxorubicin be recommended for patients at an advanced age with diffuse large B-cell lymphoma?” However, taking into account a discussion with the recommendation panel as well as the

fact that not only doxorubicin but also other anthracycline drugs such as pirarubicin are used in treating the disease, the term “doxorubicin” was replaced with “anthracycline drugs.” Furthermore, it was pointed out in external evaluation that the definition of patients at an advanced age was not clear. Therefore, such patients are now referred to as “geriatric patients aged 80 years or older.”

A literature search was conducted with the following keywords: lymphoma, large B-cell, diffuse, therapy, anthracyclines, aged 80 years and over, and doxorubicin. Sixteen papers identified through the initial screening were narrowed down to six papers[2-7] in the second screening.

In order to answer the present CQ, it is necessary to compare two groups, namely a group of subjects in whom a drug therapy with an anthracycline drug is administered and a group of subjects for whom a drug therapy with no anthracycline drug is administered. However, no prospective study with such a comparison was found in our literature search. Four retrospective studies were found, of which one was conducted in Japan, two in the United States, and one in Sweden. Two prospective cohort studies were identified, of which one was conducted in Japan[2] and one in France[3]. Both of them were single-arm, phase II studies.

Evidence for the outcomes was evaluated based on these six papers[2-7]. The prospective study in Japan looked into treatment with anthracyclines. However, the number of subjects was small at 16. Furthermore, rituximab was not used in this study, although it is a key drug in the treatment for DLBCL. One study reported that during a median observation period of 31 months, 2-year OS was 32.1% and 5-year OS was 24.6%. During a median observation period of 24 months, 2-year PFS was 32.1%, and 5-year PFS was 18.2%[1]. In a prospective, overseas multicenter study evaluating R-miniCHOP therapy, the doses of drugs other than rituximab were reduced by approximately 50%. In this study, at a median observation period of 20 months, 2-year OS was 59% (95% confidence interval [CI]: 49-67%), 2-year PFS was 47% (95% CI: 38-56%), and the complete response rate was 73% (95% CI: 65-80%)[3]. R-miniCHOP therapy was also administered in a retrospective study in a single center in Japan[4]. The study found that 2-year OS was 51%, 2-year PFS was 48%, and complete response rate was 65%. These results were similar to those of the other studies mentioned above.

It is difficult to compare and evaluate treatments that involve anthracyclines and those that do not because no randomized studies have been conducted that perform such a

comparison. However, a retrospective analysis of rituximab plus cyclophosphamide, vincristine, and prednisone (R-CVP) therapy in 43 cases that did not involve anthracycline drugs reported that 2-year OS was 32%[5]. The analysis was performed in a single, overseas facility. A retrospective analysis of cancer registration data in the United States reported that no significant difference was observed in treatment outcomes depending on the use of anthracycline drugs (hazard ratio [HR]: 0.82; 95% CI: 0.59-1.13)[6]. Another analysis reported that the survival period of patients who received R-CHOP therapy with anthracycline drugs was longer than those of patients who received CHOP therapy or R-CVP therapy (HR: 0.45; 95% CI: 0.33-0.62)[7].

In terms of cardiac toxicity, an overseas, phase II multicenter study on R-miniCHOP therapy has reported that the incidence rate of arrhythmia of grade 3 or 4 was 10% (95% CI: 6-16%) and that the incidence rate of cardiac toxicity other than arrhythmia of grade 3 or 4 was 11% (95% CI: 6-17%)[3]. A retrospective study in a single facility in Japan has reported that the incidence rate of cardiac toxicity of grade 3 or more was 0%[4]. Because no reports from randomized comparative studies are available, it is difficult to directly compare data. However, a retrospective analysis of R-CVP therapy in an overseas single facility reported that the incidence rate of cardiac events of grades 3 and 4 was 18.6%[5]. Such results may have been obtained because the subjects in this study had a poor general condition and comorbidities, including reduced cardiac function. A study on THP-COP therapy in Japan reported that the incidence rate of cardiac toxicity of grade 3 or more was 0%[2]. Pirarubicin, which is considered to cause mild cardiac toxicity, is used in THP-COP therapy.

It has been reported that the incidence rate of febrile neutropenia (FN), which is a serious adverse event, was 7-9% in patients treated with anthracycline drugs and 19% in those treated with R-CVP therapy[5]. A retrospective analysis of U.S. cancer registration data[7] reported incidence rates of FN in 595 subjects who received R-CHOP therapy as follows: 5.6% in those aged 81 years or older and 8.6% in those aged 66-80 years.[6] As the incidence rate in the former group was lower, it can be considered that administering a drug therapy with anthracycline in patients aged 80 years or older will not cause an increase in the incidence rate of FN as long as appropriate measures are taken, such as dose adjustment and prophylactic administration of granulocyte-colony stimulating factor (G-CSF). Furthermore, a prospective analysis in Japan[2] reported that no cases of treatment-related death were observed. However, an overseas, retrospective analysis

reported that the incidence rate of treatment-related death was 23% in patients who received treatment through a regimen that does not include anthracycline drugs and 15% in those who received treatment through a regimen that includes anthracycline drugs. However, no significant difference was observed between these groups. It was found through multivariate analysis that performance status was the only factor related to treatment-related death (odds ratio: 3.87; 95% CI: 1.86-8.03)[6]. A strong bias was found in treatment-related death due to differences in patient backgrounds. The variance was 0-35%.

The following tendency was observed in all studies in which evidence was evaluated: a drug therapy with anthracycline was administered for patients in good general condition who had no or mild comorbidity, and a drug therapy with no anthracycline was administered in other patients. Therefore, it is difficult to directly compare regimens that include anthracycline drugs and those that do not. It was determined that the strength of the body of evidence is "extremely low (D)."

Given the above, it is difficult to draw a clear conclusion as to whether a drug therapy that includes anthracycline can be recommended for geriatric patients aged 80 years or older with DLBCL. Various opinions suggested that it is acceptable to administer anthracycline drugs to geriatric patients aged 80 years or older as long as it is considered possible to do so from a medical point of view. However, the decision as to whether or not it is possible to administer anthracycline drugs tends to be at the doctor's discretion. No detailed indices have been developed in this regard. In conclusion, it was determined to mildly recommend administering a drug therapy with anthracycline in geriatric patients aged 80 years or older with DLBCL by carefully making a decision on the appropriateness of the therapy. This conclusion was drawn because certain patients may benefit from a standard therapy that includes anthracycline drugs.

Voting results

From among fourteen panel members, one voted for "strong recommendation for administering a drug therapy with anthracycline," eleven voted for "mild recommendation for administering a therapy with anthracycline," and two voted for "mild recommendation for not administering a therapy with anthracycline." In a post-voting discussion, it was determined to "mildly recommend (propose) administering a therapy with anthracycline."

Future research questions

Currently, the goal of treatment for DLBCL is to cure the disease. However, the values of geriatric patients vary. Therefore, it is necessary to conduct a study that adopts new outcomes based on the values of geriatric patients in addition to cure and long-term survival. Moreover, further objective indices are required to determine the appropriateness of treatment so that opportunities for curing the disease will not be lost due to underestimating such appropriateness.

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