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

Lung cancer

CQ 7

Can prophylactic cranial irradiation be recommended for older patients with small-cell lung cancer in whom a complete response has been achieved through primary therapy?

Recommendation

It is proposed that prophylactic cranial irradiation should be performed for older patients with small-cell lung cancer in whom a complete response has been achieved through primary therapy. [Strength of recommendation: 2 (rate of agreement: 77%); strength of evidence: C]

Background

1. Standard treatment for older patients with small-cell lung cancer in whom a complete response has been achieved through primary therapy

Treatment for small-cell lung cancer (SCLC) is determined based on the following factors: tumor progression (limited /extensive diseases (LD/ED), age, performance status (PS), and complications. SCLC is a tumor that is highly sensitive to chemotherapy and radiotherapy. The prolongation of survival has been observed even in older patients. A cure can be expected as long as the cancer is localized.

For patients with PS of 0-2 and normal organ function, the recommended therapy for localized SCLC is cisplatin plus etoposide combination therapy together with thoracic radiotherapy through accelerated hyperfractionation. In principle, four cycles of the therapy are administered. Further, prophylactic cranial irradiation (PCI) is recommended in patients who have achieved a complete response (CR).

2. Approach to treatment in older patients

PCI can suppress the onset of brain metastasis. It also significantly improves the prognosis. However, the late toxicity of PCI includes impaired cognitive function. Physiologically, there is a tendency for older patients to have worse cognitive function. It is likely that older patients who undergo PCI will have difficulties in their everyday lives.

Additionally, although the acute toxicity of PCI rarely causes a serious concern, chemo

radiotherapy provided as the primary therapy before PCI has extremely severe toxicity. Not every patient can complete the primary therapy as scheduled and the detailed situation how older patients are being treated is unknown.

Moreover, considering the diversity of values held by older patients, it is necessary to consider the toxicity of the treatment and respect the patient's values in relation to post-treatment sequelae, even if a treatment is selected with curative intent.

3. Concerns in clinical settings

When a recommendation for treatment is given to an older patient, it is possible to provide them with relatively accurate information on the prolongation of survival (benefit) and the incidence of adverse events and sequelae (harm). However, it is difficult to generalize the balance of such benefit and harm. Non-older patients tend to consider that the prolongation of survival is an absolute benefit, whereas this is not necessarily the case with older patients. A crucial concern for healthcare providers is how to provide the information for older patients who have diverse values. Moreover, it is difficult for a patient to link such information to their everyday life and decision-making.

Given the above, the key clinical issue was identified: "What kind of drug therapy is appropriate for SCLC in older patients?" To address this issue, the following CQ was set: "Can PCI be recommended for older patients with SCLC in whom a CR has been achieved through primary therapy?" The following setting was estimated for CQ7: a decision is to be made as to whether PCI will be performed in addition to existing therapies in an older patient for whom favorable progress has been achieved through intense chemoradiotherapy with the curative intent. In making such a decision, it is noted that PCI may slightly (25% or less) increase the possibility of a cure.

Literature review and clinical interpretation

Treatment for SCLC is determined based on the following factors: tumor progression (LD/ED), age, PS, and complications. SCLC is a tumor that is highly sensitive to chemotherapy and radiotherapy. The prolongation of survival has been observed even in older patients. A cure can be expected as long as the cancer is localized.

A recommended therapy for LD SCLC is cisplatin plus etoposide combination therapy combined with thoracic radiotherapy through accelerated hyperfractionation. It is recommended that PCI should be performed in patients who have achieved CR. PCI can

suppress the onset of brain metastasis. It also significantly improves the prognosis. However, the late toxicity of PCI includes impaired cognitive function.

Non-older patients tend to consider the prolongation of survival an absolute benefit. However, values held by older patients vary. Thus, it is important to determine whether or not PCI will be performed in an older patient with SCLC with the aim of alleviating the risk of future brain metastasis. This is particularly the case when favorable progress has been achieved in such a patient through intensive chemoradiotherapy.

Given the above, we examined whether PCI can be recommended for older patients with SCLC who have achieved CR through primary therapy. The following direct outcomes were adopted: prolongation of survival, prolongation of progression-free survival, suppression of brain metastasis, incidence of adverse events of grade 3 or more, and maintaining quality of life (QOL) (including cognitive function).

The initial screening extracted 58 papers through a systematic literature search. Subsequently, a second screening narrowed the number of papers down to seven. Of these papers, one was a randomized controlled trial (RCT) and six were observational studies. Although the RCT were not originally limited to older patients, the subgroup analysis of older patients by a Cochrane systematic review was adopted. From among six observational studies, two were not adopted as they did not conduct a subgroup analysis of older patients. One meta-analysis[1] and its Cochrane systematic review[2] were adopted as references because subgroup analyses in these papers covered a number of outcomes (overall survival and onset of brain metastasis in the following three age groups: ≤54, 55-64, and ≥65 years). After excluding other papers, five were used in creating the body of evidence: one RCT and four observational studies. The results of the meta-analysis was also considered.

One RCT was found that examined the prolongation of survival at any age; however, a subgroup analysis of older patients was not conducted in the study[3]. The Cochrane systematic review, however, conducted a subgroup analysis of the RCT by age. In the subgroup of patients aged 65 years or older, a hazard ratio was also 0.11 (95% confidence interval [CI]: 0.02-0.73). Results indicated that PCI significantly prolongs the survival period. In observational studies, the 5-year survival rates of older patients aged 73 years or older were 10% in the PCI group and 5% the non-treatment group[4]; the 2-year survival rates in patients aged 70 years or older were 33% in the PCI group and 23% in the non-treatment group[5]. The hazard ratio in older patients aged 70 years or older, including those

with ED SCLC, was 0.91 (95% CI: 0.49-1.68)[6]. Papers by Patel and Eaton are observational studies that used the SEER database. A large number of patients were examined in these studies. Thus, considering results from the above studies including the RCT, it was determined that the strength of evidence is "weak (C)." Also, in a subgroup analysis by age in the Cochrane systematic review, the hazard ratio in the group of patients aged 54 years or younger was 0.84 (95% CI: 0.65-1.08), that in the group of patients aged from 55-64 years was 0.90 (95% CI: 0.73-1.11), and that in the group of patients aged 65 years or older was 0.79 (95% CI: 0.60-1.03). Older patients were categorized as those aged 65 years or older in the analysis. Treatment outcomes in this age group were equivalent to those in the other age groups[2].

No papers that evaluated the prolongation of progression-free survival were found.

No RCTs that investigated the suppression of brain metastasis in older patients were found. Although a subgroup analysis by age was conducted in the Cochrane systematic review, the number of events was extremely small. It was difficult to interpret results based only on the review. Thus, it was determined that the strength of evidence is "extremely weak (D)." Also, in the Cochrane systematic review, the odds ratio (OR) in the group of patients aged 54 years or younger was 0.55 (95% CI: 0.39-0.77), that in the group of patients aged from 55-64 years was 0.49 (95% CI: 0.35-0.68), and that in the group of patients aged 65 years or older was 0.37 (95% CI: 0.24-0.59). Older patients were categorized as those aged 65 years or older in the review. The OR in this age group was equivalent to those in the other age groups.

No RCTs were found and only one observational study[6] was found that investigated the incidence of grade 3 or more adverse events in older patients. The numbers of events were not sufficient in the observational study. It was difficult to interpret results based only on this paper. Thus, it was determined that the strength of evidence is "extremely weak (D)."

No papers that evaluated the reduction of QOL (including cognitive function) were found.

Compared to non-older patients, the risk of the reduction of cognitive function is a more serious concern for older patients. This is because older patients have underlying, age-related cognitive impairment. If PCI deteriorates cognitive impairment in an older patient, irrespective of the degree, this may give rise to a serious concern in their everyday life. Little research has been carried out into PCI-related adverse events in older patients.

Therefore, it is impossible to quantify the risk. It is true that SCLC is an intractable disease. However, there is still a possibility of cure. That said, PCI can improve treatment outcomes only to a slight degree. It is considered that the benefit-harm balance depends on the values held by the individual patient.

Voting results

One panel member withdrew from voting due to academic conflicts of interest, and thirteen participated in voting. Of these, ten voted for "week recommendation for conducting PCI" and three voted for "week recommendation for not conducting PCI." It was determined that the strength of recommendation would be "week recommendation (proposal) for conducting PCI."

It is necessary to consider the diversity of values held by older patients to a greater extent than for non-older patients. It is natural that values vary between those who have already retired and are living a relaxed life and those who are still working and need to maintain their social status even if such people are the same age. In determining a recommendation, it is necessary to deeply consider the social situations of the older patient. Additionally, when a decision is to be made as to whether PCI will be performed or not, it is necessary for a physician to provide the patient with detailed explanations about efficacy and adverse events so that a decision can be made based on the patient's personal values.

Future research questions

It was pointed out that long-term (at least 5 years) studies on PCI-related adverse events are required. Moreover, it is considered that research into views toward life and death of older people aged 80 years or older is also required.

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CQ 8

What kind of adjuvant chemotherapy can be recommended for completely resected, early-stage non-small cell lung cancer in older patients?

Recommendation

1. It is proposed that tegafur-uracil be administered as adjuvant chemotherapy to older patients in postoperative stages IA/IB/IIA. [Strength of recommendation: 2 (rate of agreement: 79%); strength of evidence: B]

2. It cannot be clearly proposed that chemotherapy involving cisplatin-based combination chemotherapy should be administered as adjuvant chemotherapy in older patients in postoperative stages II-IIIA. [Level of recommendation: None; strength of evidence: B]

Background

1. Standard treatment for completely resected, early-stage non-small-cell lung cancer

Standard adjuvant chemotherapies for completely resected, early-stage non-small cell lung cancer (NSCLC) are as follows: tegafur-uracil (UFT) for pathological stages IA/IB/IIA (TNM classification version 8) and cisplatin-based combination chemotherapy (mainly cisplatin + vinorelbine) for pathological stages II-IIIA (TNM classification version 8). Cisplatin-based combination chemotherapy can reduce the mortality risk by approximately 10%. The 5-year survival rate is favorable at over 90% in pathological stage IA. However, as the disease stage progresses, treatment outcomes become worse and the 5-year survival rate in clinical stage III is below 50%.

2. Approach to treatment in older patients

Cisplatin-induced renal dysfunction as well as the load on cardiac function due to bolus infusion at the time of cisplatin administration are concerns in many older patients. Also, there are concerns about the enhancement of other adverse events in older patients such as nausea/vomiting and peripheral neurotoxicity. Treatment-related death occurred in approximately 1% of all cases of cisplatin-based combination chemotherapy. Because UFT is administered over the course of 2 years, it is important to maintain the patient's medication adherence during the long-term therapy. Therefore, it is critical to choose an appropriate adjuvant chemotherapy for an older patient.

Given the above, the key clinical issue was identified: "What kind of chemotherapy is

appropriate for NSCLC in older patients?" To address this issue, the following clinical question (CQ) was set: "What kind of adjuvant chemotherapy can be recommended for completely resected, early-stage lung cancer in older patients?" In order to clarify discussion points for the present CQ, the CQ was divided into the following two sub-questions: "Should the oral administration of UFT be performed over the course of 2 years for pathological stages IA/IB/IIA?" and "Should four cycles of cisplatin-based combination chemotherapy (cisplatin + vinorelbine) be performed for stages II to IIIA?"

Literature review and clinical interpretation

Standard adjuvant chemotherapies for completely resected, early-stage NSCLC are as follows: UFT for pathological stages IA/IB/IIA; and cisplatin-based combination chemotherapy (mainly four cycles of cisplatin + vinorelbine) for pathological stages II to IIIA. Cisplatin-based combination chemotherapy can reduce the mortality risk by approximately 10%. However, it is determined that the administration of cisplatin is not appropriate in most older patients. There are also concerns about the enhanced toxicity of chemotherapy in older patients. UFT is administered over the course of 2 years; therefore, UFT therapy requires a long period of time. Treatment-related death can occur in approximately 1% of all cases of cisplatin-based combination chemotherapy, which would be critical for an older patient. Given the above, the following questions were examined: whether the oral administration of UFT should be performed over the course of 2 years for pathological stages IA/IB/IIA and whether cisplatin-based combination chemotherapy should be administered for stages II-IIIA.

The following direct outcomes were adopted for the present CQ: prolongation of survival, prolongation of relapse-free survival, incidence of grade 3 or more side effects, incidence of treatment-related death, and maintaining quality of life (QOL). In order to maintain consistency between TNM classification version 8 and earlier versions, the CQ and recommendations were amended accordingly.

The initial screening extracted 90 papers through a systematic literature search. Subsequently, a second screening narrowed the number of papers down to eight. Of these, six were randomized controlled trials (RCTs) and two were observational studies. Although patients in the RCTs were not limited to older patients, a subgroup analysis of older patients was conducted in these studies. Meta-analyses in which a subgroup analysis was conducted by age were adopted as references.

The bias risk was classified as "-1" because all six RCTs are open-label studies, and their protocols are not disclosed. The indirectness of survival was classified as "-1" because a subgroup analysis by age was not conducted. The indirectness of relapse-free survival, the incidence of grade 3 or more adverse events, and the incidence of treatment-related death was classified as "-2" because a subgroup analysis was conducted in only one study. That of the maintenance of QOL was classified as "-2" because this aspect was not investigated in the RCTs but only in observational studies.

From among the RCTs on adjuvant chemotherapy for early-stage NSCLC, five conducted a subgroup analysis of survival period by age. Of these, four conducted a subgroup analysis of patients aged 65 years or older or 66 years or older[1-4]. One conducted a subgroup analysis of patients aged 60 years or older[5]. A report by Pepe et al.[3] is a subgroup analysis of an RCT on 482 patients who had undergone surgery for NSCLC of pathological stage IB or II (TNM classification version 7 or later). One hundred fifty-five patients aged 66 years or older were divided into the following two groups: a group consisting of those who received combination chemotherapy with cisplatin and vinorelbine and a control group for whom only observation was conducted. Compared with the control group, the survival period in the combination chemotherapy group was significantly longer (hazard ratio [HR]: 0.61; 95% confidence interval [CI]: 0.38-0.98). The effects of the intervention in the subgroup analysis were equivalent to those in overall patients, including 327 patients aged 65 years or younger. A small proportion of older patients completed the therapy, and a large proportion of them refused treatment. No other papers reported significantly favorable results in an intervention group. In a subgroup analysis of an RCT on patients with pathological stage I (version 7 or earlier), there was a tendency for the survival period to be prolonged in the UFT therapy group, but no significant difference was observed[2,5]. Other studies investigated with platinum-based combination chemotherapy in patients with pathological stage IB or a more advanced disease stage (version 7 or earlier). A favorable tendency was not observed in cisplatin-based combination chemotherapy but was observed in combination chemotherapy with carboplatin, although there was no significant difference[6]. Results from meta-analyses, which were adopted as references[7-9], indicate that the survival period was significantly prolonged through the oral administration of UFT. The same finding was observed even in a subgroup consisting of patients aged 70 years or older[7]. A favorable tendency was observed with cisplatin-based combination chemotherapy in a subgroup analysis of

patients aged 65 years or older; however, no significant difference was observed[8,9]. Although multiple RCTs were found, only subgroup analyses were relevant to our examination. Thus, the strength of evidence was determined to be "medium (B)."

Only one RCT conducted a subgroup analysis of relapse-free survival by age[6]. The analysis compared the effects of preoperative and postoperative adjuvant chemotherapy with carboplatin or paclitaxel and postoperative observation in patients who were diagnosed with NSCLC of clinical stage I (version 7 or earlier) or a more advanced stage. There was a tendency for the relapse-free survival to be longer in 162 patients aged 65 years or older who received postoperative adjuvant chemotherapy than that in 180 patients for whom only observation was conducted. However, no significant difference was observed (HR: 0.81; 95% CI: 0.58-1.14). Only one relevant RCT was found, and it was a subgroup analysis. Thus, it was determined that the strength of evidence is "weak (C)."

In relation to grade 3 or more adverse events, a subgroup analysis by age was conducted in one RCT[3]. Such an analysis was not conducted in the other five RCTs. In an analysis of all age strata including non-older patients, relatively mild adverse events were observed in the UFT group, whereas many adverse events of grade 3 or more were observed in the group consisting of patients who received platinum-based combination chemotherapy. It was determined that the strength of evidence is "weak (C)" because a subgroup analysis was conducted in only one RCT.

From among all papers adopted in this examination, a subgroup analysis of QOL maintenance was not conducted in any RCT and in only one observational study[10]. This was a prospective study of QOL in 139 cases (of whom 66 were 65 years old or older) who received adjuvant chemotherapy consisting of carboplatin and paclitaxel or cisplatin and vinorelbine following surgery for NSCLC of stage I or more advanced stage. No significant reduction in QOL was observed postoperatively even in patients aged 65 years or older. Changes in QOL and the degree of adverse events in these patients were equivalent to those in patients aged younger than 65 years. Only an observational study was found. Thus, it was determined that the strength of evidence is "extremely weak (D)." None of the adopted papers evaluated the incidence of treatment-related death.

A significant prolongation of survival was observed in older patients aged 70 years or older who received UFT therapy for pathological stage IA/IB/IIA. Although the therapy requires a long treatment period of 2 years, adverse events associated with the therapy are

relatively mild. It is considered that it is possible to maintain the patient's adherence at a favorable level through the therapy.

However, it has been considered that the benefit of the combination chemotherapy barely exceeds the harm because the difference in 5-year survival rate between the chemotherapy and observation for pathological stages II to IIIA is at most 10% and because the risk of serious adverse events increases following surgery and treatment-related death occurred among approximately 1% of patients in the clinical studies with non-older patients. It is necessary to carefully determine whether or not a patient who may have been cured through surgery should further receive the chemotherapy that may cause extremely severe adverse events. This is a fundamental issue with postoperative adjuvant chemotherapy.

It is necessary to consider the diversity of values held by older patients to a greater extent than for non-older patients. The risk of QOL decline as a result of adverse events is more serious for older patients than for non-older patients. An older patient may prioritize the maintenance of QOL over the prolongation of survival.

Voting results

1. UFT therapy for pathological stages IA/IB/IIA: From among fourteen panel members, one voted for "strong recommendation for administering the therapy," eleven for "mild recommendation for administering the therapy," and two 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."

2. Cisplatin-based combination chemotherapy for pathological stages II to IIIA: From among fourteen panel members, four voted for "mild recommendation for administering the therapy," eight for "mild recommendation for not administering the therapy," and two for "strong recommendation for not administering the therapy." A recommendation could not be determined. Those who voted for recommending administering the therapy indicated that they would not like to exclude a therapy that may prolong survival. Meanwhile, those who voted for not administering the therapy pointed out the following concerns: the therapeutic effects of adjuvant chemotherapy in an older patient are limited and adverse events in older patients tend to be severe. It has also been pointed out that recommending the therapy is not consistent with an existing recommendation that "single-drug" monotherapy be adopted rather than a "two-drug" combination

chemotherapy for advanced NSCLC in older patients. An additional round of voting was carried out, in which five voted for "mild recommendation for administering the therapy," five for "mild recommendation for not administering the therapy," three for "strong recommendation for not administering the therapy," and one abstention. Results from this round were more diversified than those from the previous round. A third round was not carried out, and the recommendation panel determined that there would be "no recommendation."

Future research questions

A limited number of older patients can receive cisplatin-based combination chemotherapy in real-world clinical settings. Although it is not realistic to conduct a prospective, comparative study, it is necessary to accumulate detailed, real-world data on treatment effects and adverse events in older patients. Additionally, although a recommendation related to cisplatin-based combination chemotherapy for pathological stages II to III could not be determined, an observational study[11] on older patients aged 80 years or older, which remained after the second screening, has reported that the efficacy of adjuvant drug therapy was not validated. Further research is required on this aspect.

References

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CQ 9

Can immune checkpoint inhibitor therapy be recommended for non-small cell lung cancer in older patients?

Recommendation

It is proposed that immune checkpoint inhibitor therapy be administered in older patients with non-small cell lung cancer. [Strength of recommendation: 2 (rate of agreement: 86%); strength of evidence: B]

Background

1. Standard treatment for stage IV non-small-cell lung cancer

Drug therapies for advanced non-small-cell lung cancer (NSCLC) are determined based on the following aspects: histological subtype (squamous cell carcinoma or non-squamous cell carcinoma), molecular biological markers (e.g., EGFR gene mutation, ALK fusion gene), age, performance status (PS), comorbidity, and patient preference. It is possible to expect the prolongation of survival and the improvement of quality of life (QOL) even in an older patient with an appropriate drug therapy.

Platinum-based combination chemotherapy with or without bevacizumab is one of the recommended first-line therapy for stage IV NSCLC in a patient with PS 0-1 (2) and normal organ function. A subsequent maintenance therapy with non-platinum drug could prolong survival without undermining QOL in patients in whom the tumor is well controlled at the completion of four to six cycles of the preceding chemotherapy. In recent years, a large number of efficacious drugs have been developed for NSCLC. Second-line and subsequent line therapies have now been adopted as standard treatments for a patient experiencing a relapse following the first-line chemotherapy. Until recently, docetaxel monotherapy had been a standard secondary treatment. Meanwhile, nivolumab and pembrolizumab, which are anti-PD-1 human monoclonal antibodies, have been newly marketed as immune checkpoint inhibitors. Clinical studies have found that nivolumab and pembrolizumab significantly prolonged survival compared with docetaxel. Thus, these drugs are now widely adopted in the clinic for the secondary treatment for NSCLC. Favorable treatment outcomes from atezolizumab, an anti-PD-L1 antibody, have also been reported. At present, pembrolizumab is recommended in the first-line therapy for a tumor with high positive PD-L1 expression (≥50% tumor cells). Although, one of the characteristics of immune checkpoint inhibitors is their long-term anti-tumor effects, it

has not been possible to identify groups of patients who may benefit from such effects beforehand.

2. Approach to treatment in older patients

Because no large-scale, clinical studies of the efficacy and adverse events of immune checkpoint inhibitors have been conducted specific to older patients, the detailed situation is currently not clear. According to many clinical studies including older patients, the risk of adverse events from immune checkpoint inhibitors in older patients is unlikely to be as high as that from existing cytotoxic anticancer drugs, such as cisplatin. Moreover, the frequency of adverse events is generally lower in immune checkpoint inhibitors than in cytotoxic anticancer drugs, and even if a severe adverse event occurs, such an event can be managed through an effective therapy, such as steroids, in many cases. However, the frequency and the severity of immune-related adverse events in older patients as well as their responsiveness to steroids are overall unclear. Further, if older patients have an immune-related endocrine disorder, they will need to receive hormone replacement therapy for the rest of their life. Whether this can be acceptable or not may be controversial. Additionally, as immune checkpoint inhibitors are innovative medical products, they are extremely expensive. Managing the cost of the drugs is an important issue that requires urgent attention in a nation with an aging population and a decreasing birth rate.

Given the above, the key clinical issue was identified: “What kind of drug therapy is appropriate for NSCLC in older patients? To address this issue, the following clinical question (CQ) was set: “Can immune checkpoint inhibitor therapy be recommended for NSCLC in older patients?”

Literature review and clinical interpretation

Until recently, docetaxel monotherapy had been the standard as a second-line chemotherapy for stage IV NSCLC. Meanwhile, nivolumab and pembrolizumab, anti-PD-1 human monoclonal antibodies and immune checkpoint inhibitors, are now widely adopted for standard therapies in the clinical practice. Additionally, favorable treatment outcomes from atezolizumab, an anti-PD-L1 antibody, have also been reported and the drug has also been introduced to the practice. For a tumor with a high positive PD-L1 expression (≥50% tumor cells), pembrolizumab is primarily recommended. Meanwhile,

a characteristic of immune checkpoint inhibitors is their long-term anti-tumor effects. However, at present, groups of patients who may benefit from such effects cannot be identified beforehand. Furthermore, although it is important to control immune-related adverse events, the frequency and severity of such adverse events in older patients as well as their responsiveness to steroid therapy are unclear. Given the above, we examined whether immune checkpoint inhibitors can be recommended for the treatment of NSCLC in older patients.

The following direct outcomes were adopted for the present CQ: prolongation of survival, prolongation of progression-free survival, incidence of grade 3 or more adverse events, incidence of treatment-related death, and maintaining QOL. CQ 9 was originally defined as follows: “Can anti-PD-1 antibody therapy be recommended for non-small-cell lung cancer in geriatric patients?” However, as anti-PD-L1 antibodies have also been introduced, the CQ was amended to include both the PD-1 and PD-L1 antibodies.

The initial screening extracted 19 papers through a systematic literature search. Subsequently, a second screening narrowed the number of papers down to nine. Of these, five were RCTs: one phase I study, one phase II single-arm study, and two meta-analyses. All five RCTs directly compared an intervention group (nivolumab, pembrolizumab, and atezolizumab) and a control group (cytotoxic anticancer drugs). However, none of these were limited to older patients. No subgroup analysis by age was conducted in the two meta-analyses, of which one focused on the incidence of interstitial pneumonia. Thus, it was excluded.

It was considered that the bias risk was “-1” because all five RCTs are open-label studies. The indirectness of the survival and the progression-free survival was “-1” because a subgroup analysis by age was conducted. That of the incidence of grade 3 or more adverse events and treatment-related death was considered to be “-2” because no subgroup analysis by age was conducted.

Four RCTs conducted a subgroup analysis of the survival by age. Of these, two conducted a subgroup analysis by dividing patients into the following two groups: patients aged younger than 65 years and patients aged 65 years or older[1,2]. In the other two RCTs, patients were divided into the following three groups: patients aged younger than 65 years, those aged 65 years or older and younger than 75 years, and those aged 75 years or older[3,4]. Rittmeyer et al. reported a subgroup analysis of 397 patients aged 65 years or older who were extracted from 850 patients with a previous treatment history. In

this analysis, the survival period of 190 patients in the intervention group, to whom atezolizumab was administered, was significantly longer than that of 207 patients in the control group, to whom docetaxel was administered (hazard ratio [HR]: 0.66; 95% confidence interval [CI]: 0.52-0.83). Results for this age group were equivalent to those from a subgroup analysis of patients aged younger than 65 years. Meanwhile, a study by Herbst et al., which compared pembrolizumab and docetaxel in patients with NSCLC with a previous treatment history, found a tendency of prolonged survival in the pembrolizumab-treated patients. In the other two studies, a significant difference was observed in a group of patients aged 65 years or older and younger than 75 years, but no difference was observed in the group of patients aged 75 years or older. All analyses in the RCTs are subgroup analyses. Thus, it was determined that the strength of evidence is "medium (B)."

A subgroup analysis of the progression-free survival by age was conducted in four RCTs. Two studies divided patients into the following two groups: patients aged younger than 65 years and those aged 65 years or older[1,5]. In the other two studies, patients were divided into the following three groups: patients aged younger than 65 years, those aged 65 years or older and younger than 75 years, and those aged 75 years or older[3,4]. A study reported by Reck et al. is one of the studies in which patients were divided into two groups[5]. Their study compared pembrolizumab and platinum-based combination chemotherapy in patients with NSCLC with a high positive PD-L1 expression (≥50% tumor cells) who have no previous treatment. The progression-free survival was significantly favorable in 164 patients aged 65 years or older treated with pembrolizumab (HR: 0.45; 95% CI: 0.29-0.70). On the other hand, a study of the patients with NSCLC with a previous treatment reported by Herbst et al. showed favorable survival in those treated with pembrolizumab, but the difference did not reach the level of significance[1]. A study of the patients with squamous cell carcinoma reported by Brahmer et al., divided into three groups and a significant difference was observed in the patients aged 65 years or older and younger than 75 years, whereas not in those aged 75 years or older[4]. A study of patients with non-squamous cell carcinoma reported by Borghaei et al. found no significant difference in the progression-free survival among the subgroups divided by age[3]. Because these analyses are subgroup analyses of RCTs, the strength of evidence was determined as "medium (B)."

None of the 5 RCTs conducted the subgroup analysis of grade 3 or more adverse events

by age. The adverse events were more likely to occur in the control group than in the intervention group in all the patients in those studies. Because the subgroup analysis was not conducted, it was determined that the strength of evidence is “weak (C)”.

None of the 5 RCTs conducted the subgroup analysis of the incidence of treatment-related death by age, although the incidence rate of treatment-related death in all the patients varied between studies. Because the subgroup analysis was not conducted, it was determined that the strength of evidence is “weak (C).”

There were not studies that evaluated the maintenance of QOL.

The age subgroup analysis of survival, which are of benefit to patients, was conducted in the 4 RCTs. The results varied as follows: one RCT found a significant prolongation of survival in the patients treated with immune checkpoint inhibitors compared with cytotoxic drugs; another found a tendency for prolongation of survival that was not significant; and the others found a significant difference in a subgroup of patients aged 65 years or older and younger than 75 years but did not in those aged 75 years or older. The differences in the analyses with negative results may have been harbored because of an insufficient number of patients. The degree of difference in progression-free survival is smaller than that in the survival, which may reflect a characteristic of immune checkpoint inhibitors that their anti-tumor effects continue for a long time. Furthermore, it should be noted that survival benefit is generally smaller in any treatments in older patients than in non-older patients.

Meanwhile, there was no age subgroup analysis of the incidence of grade 3 or more adverse events, the incidence of treatment-related death, and QOL. The frequency and severity of adverse events from cytotoxic anticancer drugs are generally high in older patients. It is unclear whether or not this applies to immune checkpoint inhibitors.

Medical expenses would not be considered either on an individual or a social basis in determining the recommendation.

Voting results

From among fourteen panel members, four voted for “strong recommendation for immune checkpoint inhibitor therapy,” eight voted for “mild recommendation for immune checkpoint inhibitor therapy,” and two voted for “mild recommendation for not administering immune checkpoint inhibitors.” A recommendation could not be determined. It was pointed out that immune checkpoint inhibitors should not be strongly

recommended because currently, there are no reliable biomarkers for predicting the efficacy of immune checkpoint inhibitors, and the efficacy may have been observed in less than half the patients treated. However, it was also indicated that it should be considered that there have been increasing expectations of therapy for patients with intractable cancer through a new mechanism. Voting was again conducted following the discussion. In this round, the number of panel members who voted for "strong recommendation for immune checkpoint inhibitor therapy" decreased to one, the number who voted for "mild recommendation" increased to twelve, and the number who voted for "mild recommendation for not administering immune checkpoint inhibitors" decreased to one. It was determined that the level of recommendation would be "mild recommendation (proposal) for immune checkpoint inhibitor therapy."

Future research questions

Although it is necessary to conduct a prospective study on immune checkpoint inhibitors in older patients with cancer, such clinical studies are not scheduled at present. However, when the combination therapy with immune checkpoint inhibitors and cytotoxic anticancer drugs has become the standard of care soon, toxicity profiles will change substantially, especially in older patients and, therefore, prospective clinical studies for older patients are required. Furthermore, after the recommendation for this CQ was determined, results from an extended access program for nivolumab for 371 patients with non-squamous cell carcinoma in Italy were published[6]. Tumor shrinkages in 175 patients aged 65 years or older and younger than 75 years (47% of the study population) and 70 patients aged 75 years or older (19% of the study population) were almost equivalent to those in 126 patients aged younger than 65 years (34% of the study population) (18%, 19%, and 18%, respectively). The incidences of grade 3 or 4 adverse events were low in all the groups (9%, 3%, and 3%, respectively). It was also reported that the treatment discontinuation rates due to adverse events were 4-5%.

In addition, immune checkpoint inhibitors are extremely expensive as they are innovative medical products. Although a scheme for reimbursing high medical expenses to patients is available in Japan (High-Cost Medical Expense Benefit), there still be a heavy burden for older patients. Managing the medical cost of drugs within the social security system is an important issue that requires urgent attention in a nation with an aging population and a decreasing birth rate like Japan.

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