Definitive concurrent chemoradiotherapy in a patient with stage IV non-small cell lung cancer due to cervical lymph node metastases

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Abstract

In the American Society of Clinical Oncology guideline, it is mentioned that systemic therapy is a standard treatment, but there is no cure for patients with stage IV non-small cell lung cancer (NSCLC). Recent technical advances have facilitated the delivery of curative-intent radiation doses to some stage IV patients. In this report, we introduce a long-term disease-free survivor after concurrent chemoradiotherapy (CRT) and discuss considerations for this treatment. The patient was a 61-year-old woman diagnosed with stage IV adenocarcinoma of the lung classified as cT4N3M1c; the M1c classification was because of multiple synchronous pathologically proven cervical lymph node metastases (CLNM). We administered concurrent CRT to all lesions with a dose of 60 Gy in 30 fractions over 6 weeks. Concurrent chemotherapy consisted of two cycles of carboplatin and pemetrexed. Adjuvant chemotherapy was performed with five cycles of carboplatin and pemetrexed followed by three cycles of pemetrexed alone. As of 43 months after CRT, the patient was still alive without disease. In conclusion, our patient with stage IV NSCLC due to CLNM achieved long-term disease-free survival by concurrent CRT as with patients with locally advanced NSCLC. Patient subgroups should be explored to achieve long-term disease-free survival after definitive CRT in patients with stage IV NSCLC due to CLNM.

Keywords Radical · Concomitant · Chemoradiation · Advanced · Lung carcinoma

Introduction

In the American Society of Clinical Oncology guideline, it is mentioned that systemic therapy is a standard treatment, but there is no cure for patients with stage IV non-small cell lung cancer (NSCLC) [1]. Recent technical advances have facilitated the delivery of curative-intent radiation doses to some stage IV patients and de Boer et al. reported the results of definitive chemoradiotherapy (CRT) for patients with stage IV NSCLC due to cervical lymph node metastases (CLNM) [2]. In their report, a patient achieved long-term disease-free survival at 43 months after sequential CRT. In

contrast, concurrent CRT is a standard curative-intent treatment for patients with locally advanced NSCLC [3]. Our report describes a long-term disease-free survivor following concurrent CRT and discusses our considerations of the factors associated with long-term disease-free survival.

Case report

The patient was a 61-year-old woman with a Karnofsky performance status (KPS) of 90. She was a former smoker with 28 pack-years. She was diagnosed with stage IV adenocarcinoma of the lung classified as cT4N3M1c according to the TNM 8th edition (Fig. 1a); the M1c classification was because of multiple synchronous pathologically proven CLNM. Epidermal growth factor receptor (EGFR) mutation was not detected. Anaplastic lymphoma kinase (ALK) or ROS1 gene rearrangement, BRAF mutation, and programmed death-ligand 1 (PD-L1) expression were not tested because cytotoxic chemotherapy was the standard first-line therapy regardless of these factors at that time. First, we

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Fig. 1 Positron emission tomographic images **a** before and **c** after chemoradiotherapy, and **b** radiation dose distribution

informed the patient that systemic therapy with a platinum-doublet regimen was the standard treatment. Next, we told her that concurrent CRT with a platinum-doublet regimen according to locally advanced NSCLC might be an option because we could deliver a curative-intent radiation dose to all lesions by enlarging a part of the radiation field compared to that of locally advanced NSCLC, although there was no evidence for its effectiveness in stage IV NSCLC. She selected to receive concurrent CRT with a dose of 60 Gy in 30 fractions over 6 weeks (Fig. 1b). The gross tumor volume (GTV) and planning target volume (PTV) were 95 and 777 cm³, respectively. Concurrent chemotherapy consisted of 2 cycles of carboplatin (area under the curve = 5) on day 1 and pemetrexed (500 mg/m²) on day 1, every 4 weeks. The acute toxicities relative to concurrent CRT according to Common Terminology Criteria for Adverse Events v4 were Grade 2 neutropenia, anemia, thrombocytopenia, anorexia, esophagitis, and dermatitis, from which she recovered. Adjuvant chemotherapy was performed including 5 cycles of carboplatin and pemetrexed and then 3 cycles of pemetrexed alone. As of 43 months after CRT, she was still alive without disease (Fig. 1c) and had only Grade 1 myalgia of the left shoulder as a late toxicity.

Discussion

Our patient with stage IV NSCLC due to CLNM achieved long-term disease-free survival by concurrent CRT as with patients with locally advanced NSCLC.

In the setting of definitive CRT for patients with stage IV NSCLC due to CLNM, de Boer et al. reported that PTV > 700 cm³ have been associated with worse outcomes

[2]. However, in the report, a patient with a PTV of 925 cm³ achieved long-term disease-free survival at 43 months. In our experience, a long-term disease-free survivor also had PTV > 700 cm³; therefore, this factor might not always be associated with long-term disease-free survival in patients with stage IV NSCLC due to CLNM. On the other hand, in de Boer's report [2], among the 10 deceased of 14 patients, 6 had an overall survival < 12 months, and 9 progressed after ≤ 10 months. The prognosis of the majority of the patients with stage IV NSCLC due to CLNM was poor. Moreover, in our patient, Grade 2 neutropenia, anemia, thrombocytopenia, anorexia, esophagitis, and dermatitis occurred as the acute toxicities. Adding RT placed additional burdens on the patients, including esophagitis and dermatitis. Therefore, we need to explore patient subgroups to derive the benefit of CRT even if we experienced a long-term disease-free survivor treated with CRT.

If not limited to only CLNM, the prognostic factors for definitive CRT have been reported in patients with stage IV NSCLC because of synchronous oligo-metastases [4]; although the factors were not for disease-free survival, GTV ≤ 124 cm³, radiation dose ≥ 63 Gy, and KPS > 80 were prognostic factors for overall survival in multivariate analyses. GTV ≤ 124 cm³ and KPS > 80 are consistent with those of our patient.

Other prognostic factors regardless of CRT have been reported in patients with radically treated oligometastatic NSCLC [5]; KPS of 90, thoracic stage I, metastases except for the brain, and involved organ of 1 were prognostic factors for progression-free survival in univariate analyses. KPS of 90, metastases except for the brain, and involved organ of 1 are consistent with those of our patient.

However, systemic therapy is a standard treatment for patients with stage IV NSCLC [1]. A meta-analysis showed the benefit of cytotoxic chemotherapy as a prognostic factor to improve survival compared with the best supportive care for patients with advanced NSCLC [6]. Recently, depending on PD-L1 expression and driver gene mutations such as EGFR-sensitizing mutation and ALK or ROS1 gene rearrangement, immune checkpoint inhibitors such as pembrolizumab and tyrosine kinase inhibitors have been superior to cytotoxic chemotherapy as the first-line therapy for patients with stage IV NSCLC [1]. Moreover, in patients with previously untreated metastatic nonsquamous NSCLC without EGFR or ALK mutations, the addition of pembrolizumab to cytotoxic chemotherapy resulted in significantly longer overall survival than chemotherapy alone regardless of PD-L1 expression [7]. The treatment for patients with stage IV NSCLC has been progressing.

In contrast, patients with locally advanced NSCLC have benefitted from the administration of immune checkpoint inhibitors such as durvalumab [8], with significantly longer progression-free survival by approximately 11 months compared to that with placebo after CRT. The treatment for patients with locally advanced NSCLC has been also progressing. To achieve cure even in patients with stage IV NSCLC, we need to explore patient subgroups to derive the benefit of treatment advances such as CRT followed by durvalumab for patients with stage IV NSCLC.

In conclusion, our patient with stage IV NSCLC due to CLNM achieved long-term disease-free survival by concurrent CRT as with patients with locally advanced NSCLC. On the basis of the above-mentioned factors, further exploration of patient subgroups is needed to achieve long-term disease-free survival after definitive CRT in patients with stage IV NSCLC due to CLNM.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in this report involving the human participant were in accordance with the ethical standards of the institutional committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This report does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from the individual participant included in this report.

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