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Case Report
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A Clinical Case Analysis of Lung Large Cell Neuroendocrine Tumor

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Abstract

Introduction: Large Cell Neuroendocrine Carcinoma of the Lung (LCNEC) is a rare and aggressive tumor with a short median survival, mainly due to limited effective treatments. Although Immune Checkpoint Inhibitors (ICIs) have revolutionised the treatment of solid tumors mode, but so far, research on ICI therapy LCNEC is still in its infancy.

Case Presentation: We report on a 61-year-old man who was diagnosed with advanced right lung large cell neuroendocrine carcinoma after surgery, through systemic treatment with immune + chemotherapy, radiotherapy for local bone metastases and radiotherapy for postoperative residual lesions, after immune maintenance therapy, the survival time has reached 24 months, during which no tumor recurrence and metastasis was found.

Conclusions: Immunotherapy combined with chemotherapy may provide a new treatment modality for patients with advanced large cell neuroendocrine carcinoma of the lung.

Keywords: Lung large cell carcinoma; Neuroendocrine tumor; Immunotherapy

Introduction

Large Cell Neuroendocrine Carcinoma of the lung (LCNEC) is a relatively rare and highly aggressive neuroendocrine neoplasm that accounts for about 3% of primary lung cancers [1], the prognosis is poor, the distant metastasis rate is high, and the 5-year Overall Survival (OS) rate is about 15% to 25%, most LCNEC patients are initially diagnosed with stage III to IV, and the 5-year OS rate in advanced patients is almost zero. The advent of the immune era has changed the treatment mode of patients with Non-Small Cell Lung Cancer (NSCLC) and benefited their survival. However, LCNEC is still dominated by chemotherapy. However, the optimal chemotherapy regimen is still controversial. Small Cell Lung Cancer (SCLC) chemotherapy regimen may be a better option, but OS benefits are poor, about 8 to 16 months in different studies [2]. Immunotherapy has been a breakthrough therapy in the treatment of NSCLC in recent years, and has become the standard of care for advanced NSCLC, either alone or in combination with chemotherapy [3,4]. However, whether immunotherapy has a survival benefit for LCNEC patients and the optimal treatment mode for LCNEC remains unclear, and more studies are needed to draw conclusions.

Case Presentation

The patient, male, Yuan XX, 61 years old, he was admitted to hospital because of "more than 20 days after surgery for lung cancer". He has a history of smoking for more than 45 years, with an average of 1-3 packs per day, and has not quit smoking. He has a drinking history of more than 45 years, with an average of 400 ml to 500 ml per day, and has not given up drinking. The patient underwent chest CT during physical examination in Yidu Hospital of Traditional Chinese Medicine on June 20, 2022. CT findings: Right upper lung nodules, puncture biopsy recommended. CEA 15.61 ng/ml." Thoracoscopic right lung lobectomy + lymph node dissection" under general anesthesia on July 1, 2022. The operation was successful. Postoperative examination: large cell neuroendocrine carcinoma, spread in alveolar cavity (+), vascular carcinoma thrombus (+), no definite nerve invasion was observed. Carcinoma infiltration was found in the lung incisal margin of bronchial rupture. Lymph nodes were examined (11/18 metastases). The postoperative stage was pT2N3M0. On July 26, 2022, the patient was admitted to the Cancer Hospital of the Second People's Hospital of Yichang City for further treatment. After surgery, the patient began to develop pain in the right lower limb with weakness, and the bone pain score of the right lower limb was 3 points, administer paracetamol oxycodone tablet 325 mg orally once /6 hours, pain control is OK. On July 30, 2022, one cycle of "EP regimen chemotherapy" was performed. In August 2022, he was

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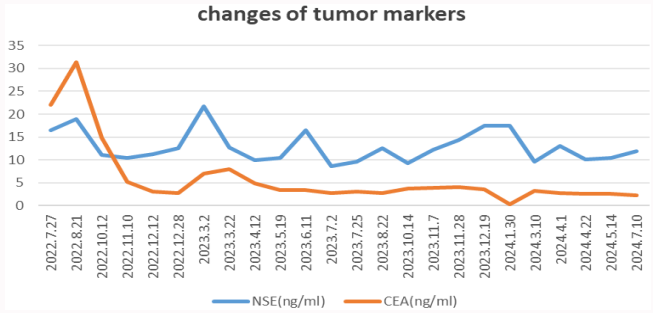

Figure 1: Changes of tumor markers CEA and NSE during hospitalization.

readmitted to hospital for systemic chemotherapy, however, due to the severe pain of the patient's right hip, oral analgesic drugs were not well controlled. Pelvic CT with contrast on 25 August 2022 showed right iliac metastases, therefore, local radiotherapy was given after consultation with the patient's family, radiotherapy to the right hip was performed from August 26 to September 20, 2022. Adjunct with pain relief (Oxycodone hydrochloride sustained release tablet 20 mg g12h, and reduced to 10 mg g12h), defecation and symptomatic support treatment. On September 22, 2022, Nivolumab immunotherapy was performed once. The patient's right hip pain improved significantly after radiotherapy, and the use of painkillers was discontinued. On October 18, 2022 and November 11, 2022, the regimen of "nivolumab +EP chemotherapy" were treated for 2 cycles, bone marrow suppression I°. The patient had residual tumor in the stump after surgery, indicating radiation therapy. Postoperative radiotherapy was performed from January 2 to February 8, 2023. Nivolumab 360 mg immune maintenance therapy started on February 10, 2023 until June 2023, liver function is impaired. Change toripalimab 240 mg immunotherapy on July 31, 2023. In August 2023, the patient came to the hospital to check the elevation of hypersensitive troponin I, the cause was unknown, the myocardial enzyme spectrum was normal, and it could not be ruled out that it was related to immunotherapy, so immunotherapy was suspended and dynamic observation was made. Contraindications were excluded in October 2023. On October 17, 2023, 240 mg immunotherapy with triplizumab (q21d) was initiated. The next treatment will be in May 2024 On the 16th, at present, the patient's condition is stable, and there has been no recurrence and metastasis during the review.

Discussion

Studies [5] have shown that patients' age at first diagnosis, gender, tumor stage, surgery, chemotherapy and radiotherapy are related to OS in LCNEC patients. Surgical treatment is still preferred for patients with resectable LCNEC, the optimal treatment strategy for locally advanced or metastatic unresectable LCNEC remains unclear. According to relevant guidelines (e.g. ASCO), the traditional treatment regimen for advanced LCNEC is similar to that for SCLC, with platinum-based chemotherapy [6]. Patients may receive chemotherapy regiments for SCLC (etoposide + platinum), or chemotherapy regiments for NSCLC. Overall, LCNEC is more aggressive than NSCLC and has a poorer response rate to standard chemotherapy regimens for SCLC. With the rise of immunotherapy, immunotherapy has made rapid progress in the treatment of advanced lung cancer patients, greatly improving the survival of patients. Despite the lack of prospective data on the use of Immunological Agents (ICIs) by LCNEC, many studies have analyzed the use of immunotherapy in LCNEC patients, providing a window for exploring the efficacy of immunotherapy. The incidence of LCNEC is low, and it is difficult to carry out prospective clinical studies. Therefore, the therapeutic effect and optimal treatment mode of immunotherapy in LCNEC are still unclear. Meng L conducted a real-world study, twenty-four patients with stage IV LCNEC from the Moffitt Cancer Center database who received systemic therapy between January 2016 and May 2021 were included. Group A received first-line chemotherapy combined with immunotherapy, and group B received first-line chemotherapy alone. The results suggest that the combination of immunotherapy and chemotherapy may improve the prognosis of stage IV LCNEC. Although the study was retrospective and had a limited sample size, these preliminary findings provide valuable insights into the potential of immunotherapy in the treatment of LCNEC and need to be further investigated through larger prospective trials [7]. Also, Sherman evaluated the activity and safety of ICIs in 37 patients with stage III and IV LCNEC, 23 of whom received immunotherapy, and no advantage of immunotherapy over conventional therapy has been observed [8]. On the contrary, a retrospective analysis examined ICI outcomes in 125 patients with stage III and IV LCNEC, forty-one of these patients received ICI as any line of treatment and reported a significant positive effect of ICI on the OS of advanced LCNEC [9]. Komiya used data from the National Cancer Database (NCDB) to assess the impact of ICI on OS in patients with stage IV LCNEC, revealing the association between ICI use and improved OS [10].

Conclusion

LCNEC is a rare and highly malignant subtype of lung cancer, and its treatment strategies still need to be further explored and optimized. Currently, surgery is the preferred treatment for early-stage LCNEC, and therapies such as adjuvant chemotherapy, radiotherapy, and immunotherapy may play an important role in improving patient outcomes. LCNEC is a rare malignant tumor with a high degree of malignancy and poor prognosis, and the recurrence rate of early patients is still relatively high. The patient, who went from receiving combination immunochemotherapy to immune maintenance therapy, achieved a Partial Response (PR) during the follow-up evaluation, demonstrating the continued effectiveness of combination immunochemotherapy for LCNES. The lesson of this case for me is this that reasonable postoperative adjuvant therapy plays a big role, however, how to choose the program and when to intervene in treatment is still worth discussing. The treatment of locally advanced or metastatic LCNEC can be considered chemotherapy, immunotherapy, targeted therapy, etc., but whether combination therapy can benefit patients' survival longer needs more prospective studies to verify! In the future, with a deeper understanding of LCNEC's molecular characteristics and biological behavior, as well as more clinical studies, we are expected to provide patients with more accurate and effective treatment options.

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