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Case report

Efficacy of Disitamab Vedotin in a heavily pre-treated HER2 positive lung adenocarcinoma patient: case report and literature review

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ABSTRACT

Cancer therapies targeting human epidermal growth factor receptor 2 (HER2) have been attracting increasing attention worldwide, especially in lung adenocarcinoma. Disitamab vedotin is an antibody-drug conjugate designed for targeting HER2 that has been approved for urothelial carcinoma and gastric cancer. However, there is still a lack of clinical evidence for applying Disitamab vedotin in lung adenocarcinoma. Herein, we reported a case of a 52-year-old man with advanced lung adenocarcinoma carrying HER2 amplification as well as HER2 immunohistochemistry (IHC) 2 + who underwent treatment with Disitamab vedotin after disease progression. The patient was treated with chemotherapy, anti-angiogenesis therapy, and immunotherapy as first-line therapy, achieving a remarkable progression-free survival of 16 months. After the disease continued to continuous progress, the patient was administrated with Disitamab vedotin, which resulted in improvement of both the lung lesions and the brain lesions. Our findings provide a valuable reference for the utilization of Disitamab Vedotin in HER2 IHC2+ lung adenocarcinoma.

1. Introduction

According to the latest global cancer statistics (Sung et al., 2021), lung cancer is the second most diagnosed cancer worldwide and the leading cause of cancer-related death. Lung adenocarcinoma is the most common subtype of lung cancer, accounting for more than 40% of all lung cancer cases (Zheng, 2016). With the development of genetic testing technology, lung adenocarcinoma came to be considered a disease strongly associated with driven genes. Known driven genes of lung adenocarcinoma include *EGFR*, *ALK*, *KRAS*, *ERBB2*, *MET*, etc. An increasing understanding of these genes substantially contributes to diagnosing lung adenocarcinoma and developing new drugs.

Human epidermal growth factor receptor 2 (HER2) is an EGFR family member encoded by the *ERBB2* gene and is situated in the chromosomal region 17q11.2-q12 (Citri and Yarden, 2006). HER2 alterations include amplification of the gene, overexpression of the protein, and mutation of the gene, where de novo and acquired gene amplification account for 3% and 13%, respectively, while protein overexpression contributes to 2%, and gene mutations are responsible for 3% of non-small cell lung cancers (NSCLC) (Yoshizawa et al., 2014; Zhao and Xia, 2020).

The HER2 protein is the mediator of intracellular signaling pathways and extracellular signals. The activation of HER2 leads to the phosphorylation of intracellular, which in turn causes the awakening of PI3K/AKT and MEK/ERK signaling pathways and stimulates cell proliferation and migration. Abnormally expressed HER2 protein is regarded not only as a driven factor of lung cancer but also as a potential therapeutic target (Zhao and Xia, 2020). Inhibitors designed for HER2 mainly contain pan-HER TKIs, anti-HER2 moAbs, and anti-HER2 antibody-drug conjugates (ADC). Although previous clinical applications of pan-HER TKIs and anti-HER2 moAbs have not shown satisfactory efficacy in NSCLC, remarkable anti-tumor effects were observed in phase I and II trials of anti-HER2 ADCs (Melosky et al., 2021).

Disitamab vedotin is an ADC therapeutic that consists of a monoclonal antibody against HER2 coupled to the cytotoxic compound

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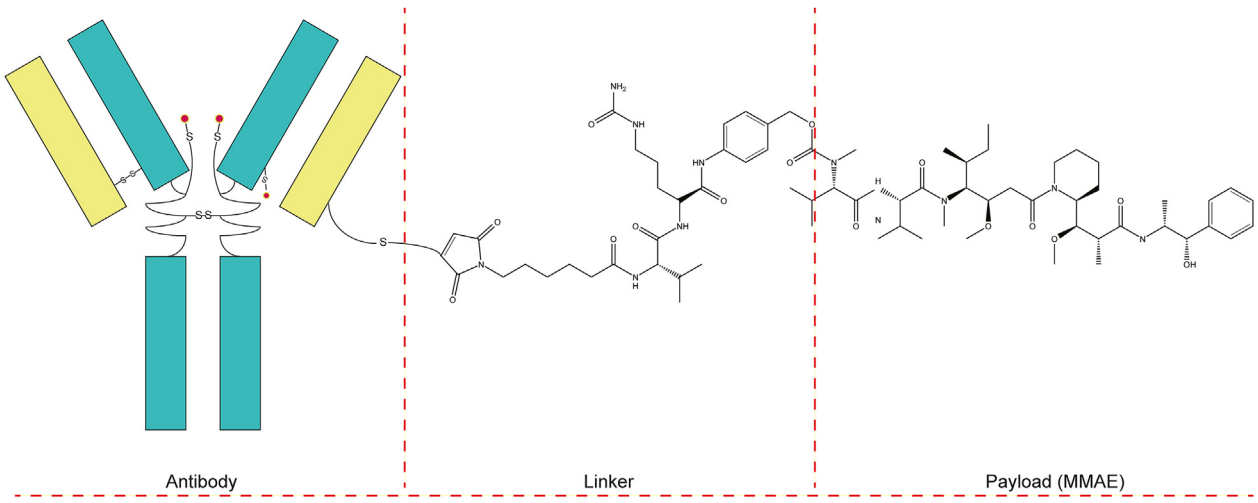

Figure 1. The molecular structure of Disitamab vedotin. Disitamab vedotin is composed of a monoclonal antibody against HER2 coupled to the cytotoxic compound monomethyl auristatin E via a cleavable linker.

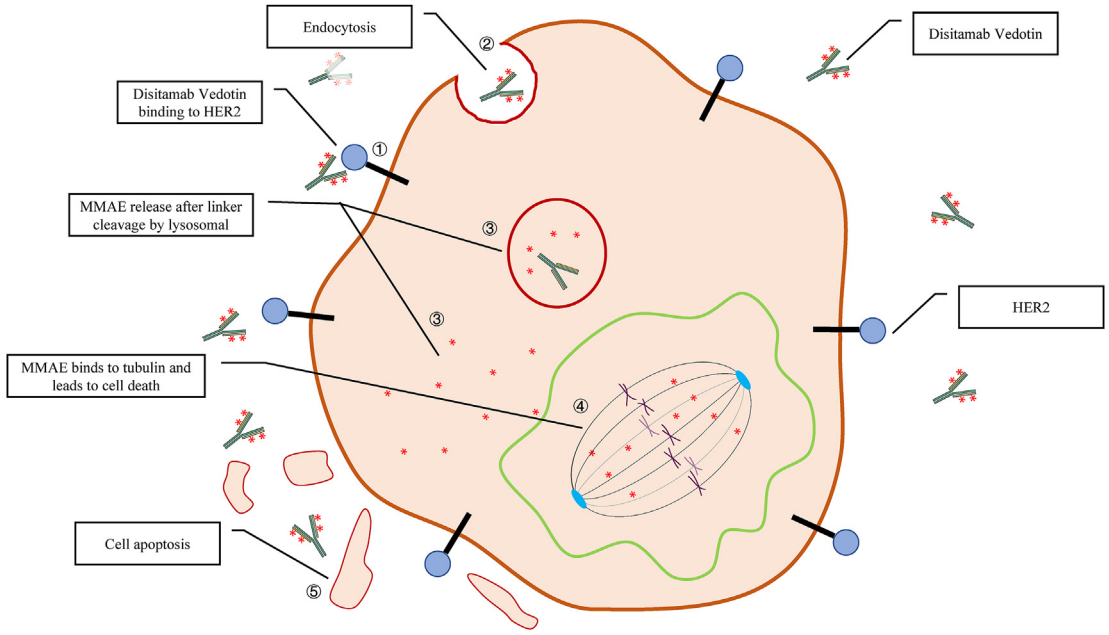

Figure 2. The anticancer mechanism of Disitamab vedotin. Upon binding to HER2 on the cancer cell surface, Disitamab vedotin is endocytosed and undergoes lysosomal degradation. Subsequently, MMAE is released and inhibits tubulin to achieve cytotoxic effects.

monomethyl auristatin E via a cleavable linker (Deeks, 2021). The molecular structure and action mechanism of Disitamab vedotin was presented in Figures 1 and 2. Disitamab vedotin has been successfully approved for patients with urothelial carcinoma overexpressing HER2 with an ORR rate of 51.2% and a median PFS of 6.9 months (Sheng et al., 2021) and as a third-line treatment for locally advanced or metastatic gastric cancer with HER2-overexpression in China (Peng et al., 2021). However, clinical trials of Disitamab vedotin for HER2 overexpression or HER2-mutated NSCLC patients are currently in the status of "Active, not recruiting" (NCT04311034). Therefore, there is still no essential evidence to support the application of Disitamab vedotin for NSCLC.

Herein, we reported on the efficacy of Disitamab Vedotin in HER2-positive lung adenocarcinoma patients whose disease progressed after chemotherapy and immunotherapy.

2. Case presentation

2.1. Chief complaints and family history

A 52-year-old male chronic smoker (twenty cigarettes a day for more than 30 years) was referred to our hospital's department in June 2018. The patient complained of shortness of breath, palpitations, and tightness, and he denied having a family history of cancer.

2.2. Imaging examinations and laboratory examinations

Enhanced computed tomography (CT) of the chest revealed two masses, one was 34 × 54mm in the left upper lobe, and the other was 28 × 24 mm in the right upper lobe. Numerous enlarged lymph nodes were found in the bilateral hilum and mediastinum, where the biggest one

measured 34 × 28 mm. Brain magnetic resonance imaging (MRI) showed extensive brain metastasis in the frontal lobe, cerebellum, and so on. The largest lesion diameter in the bilateral frontal lobe was 13 mm. Abdominal and pelvic magnetic resonance did not show any occupied lesion. The neutrophils/(leukocytes minus neutrophils) ratio (dNLR) was 3.95 and lactate dehydrogenase was 466 U/L.

2.3. Final diagnosis

The patient underwent a lymph node biopsy, and his pathological diagnosis was infiltrating, moderately to poorly differentiated adenocarcinoma. The immunohistochemistry (IHC) analysis showed that tumor cells were positive for CK, NapsinA, TTF-1, and P63, and the patient was diagnosed with advanced lung adenocarcinoma. A high expression of PD-L1 with a tumor cell proportion score of 75% was also identified. A genetic test revealed negative alterations of *EGFR*, *ALK*, *ROS1*, *MET*, and *BRAF V600E* and positive *KRAS G12A* mutation.

2.4. Treatment

The patient initially underwent 6 rounds of immunotherapy combined with chemotherapy with the specific drugs pemetrexed, carboplatin, bevacizumab, and pembrolizumab from May to September 2018. The chest CT showed satisfactory responses, with the masses measuring 17 × 12mm in the left upper lobe and 14 × 8 mm in the right, while the biggest enlarged lymph nodes decreased to 15 × 10mm. The baseline brain lesions were unmeasurable. The efficacy evaluation was established as a partial response according to the Response Evaluation Criteria in Solid Tumors 1.1.

Next, the patient underwent maintenance treatment with pemetrexed, bevacizumab, and pembrolizumab till June 2019. Considering the regular chest CT and brain MRI in June 2019 revealed no evidence of progression, the therapy was changed to pemetrexed and bevacizumab. However, the chest CT in September 2019 indicated larger lesions measuring 40 × 29 mm in the left upper lobe and 23 × 15 mm in the right, while the lymph nodes in the hilum and mediastinum and the lesion in the brain were unmeasurable. Considering the continuous progressive condition, the therapy was changed to pemetrexed, bevacizumab plus pembrolizumab in September 2019, and albumin-bound paclitaxel, bevacizumab, carboplatin plus pembrolizumab in December 2019. The chest CT obtained in March 2020 revealed a mild reduction of lung lesions when compared to the chest CT from December 2019.

To formulate a personalized treatment for the patient, a next-generation sequencing test of circulating tumor DNA was conducted, and the results showed that *HER2* gene amplification and *KRAS G12A* mutation were positive, and the tumor mutational burden was 3.35Mut/Mb. Next, the patient agreed to treatment with anlotinib and pembrolizumab. Although the chest CT in May 2020 suggested tumor shrinkage that measured 36 × 32 mm in the left upper lobe and 22 × 15 mm in the right, the patient stopped the treatment because of diarrhea and an oral ulcer he could no longer tolerate. The initial four-drug combination therapy was given again based on the satisfactory effect of the first-line treatment. Yet, the tumor revived quickly as the chest CT in August 2020 indicated that the tumor lesions in the lung significantly increased, measuring 45 × 29mm in the left upper lobe and 9 × 12mm in the right. A left upper lobe lesion biopsy, which was conducted in October 2020, suggested poorly differentiated adenocarcinoma. The IHC results indicated HER2 IHC2+ and c-MET IHC2+. The IHC result for HER2 was shown in Figure 3. The patient underwent Durvalumab plus chemotherapy with docetaxel, carboplatin, gemcitabine, paclitaxel liposome, bevacizumab, and anlotinib, among which bevacizumab was discontinued due to recurrent hemoptysis. Unfortunately, the treatment was not feasible, and the lung lesion kept increasing in volume (74 × 61 mm in the left upper lobe and 12 × 9 mm in the right in March 2021). The chest CT in July 2021 revealed larger lesions measuring 93 × 65 mm in the left upper lobe and 11 × 6mm in the right. The patient did not agree to an brain MRI examination at that time.

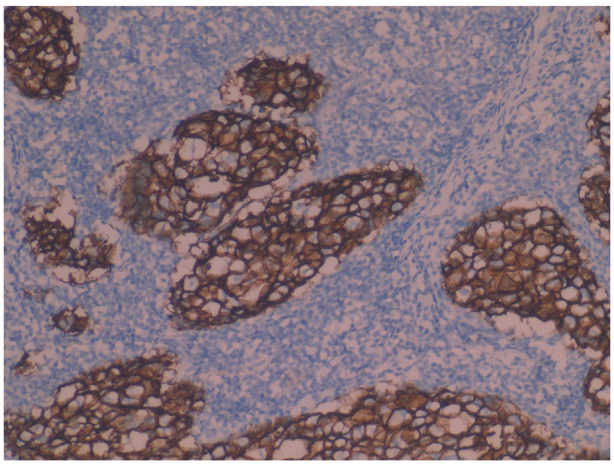

Figure 3. IHC results of HER2 in this patient.

2.5. Administration of Disitamab Vedotin

Due to the past treatment failures, we turned to new drugs based on HER2 status as the patients were positive for *HER2* amplification in the circulating tumor DNA test and HER2 IHC2+ in the IHC test of tumor tissue of the left upper lobe. We clearly and comprehensively communicated with the patient about his condition and explained the pros and cons of using Disitamab vedotin. After obtaining his consent, the administration of the drug was started. The patients received Disitamab Vedotin at a dose of 120 mg every 21 days between July 2021 and December 2021. On the one hand, the chest CT result obtained in September 2021 revealed encouraging results suggesting that the lung lesions were reduced (76 × 41mm in the left upper lobe and 11 × 6mm in the right). On the other hand, the brain MRI revealed a new lesion in the cerebellum measuring 22 × 18 mm, whose exact time of occurrence was impossible to establish. The brain MRI and chest CT in November 2021 suggested that the lesion in the cerebellum decreased to 12 × 8 mm, the lesion in the left upper lobe shrunk to 72 × 54 mm, the lesion in the right upper was stable, whereas a new lesion measuring 26 × 24 mm occurred in the dorsal segment of the lower lobe of the left lung. The same check-in in December 2021 revealed the two lesions in the left lung congregated and fused (84 × 57 mm), standing for the progression of disease once again, while the lesions in the right upper lobe (11 × 6 mm) and cerebellum (15 × 10mm) remained stable. After that, the patient came back in January 2022 seeking supportive care without the administration of Disitamab vedotin. Unfortunately, the patient did not return and died in May 2022.

Above all, there were no adverse events throughout the Disitamab Vedotin treatment. A flow diagram (Figure 4) was used to present the treatment and efficacy evaluation process.

2.6. Symptoms and performance status

At the first visit, the patient presented with mild-moderate symptoms, including shortness of breath, palpitations, chest tightness, paroxysmal cough, and sputum production. According to the Karnofsky Performance Scale (KPS), his performance status was 80. After symptomatic treatment as well as anti-tumor therapy, the patient's symptoms were relieved, and the KPS score was 90. He only complained of mild paroxysmal cough and sputum production from October 2018 to May 2020. However, as the disease progressed, these symptoms worsened again, and the KPS score did not decrease. At the beginning of 2021, hemoptysis appeared and even worsened after using bevacizumab, while KPS was 70. Thus,

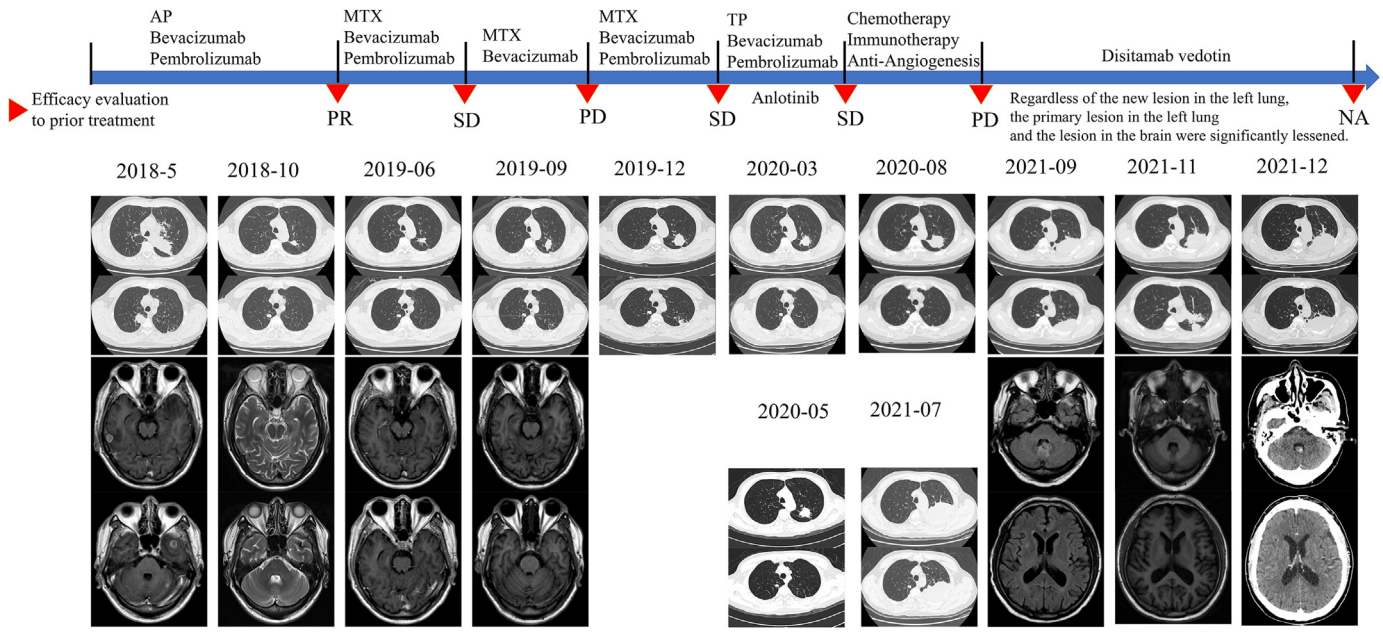

Figure 4. Treatment course chart and efficacy evaluation.

bevacizumab was discarded, and hemoptysis was diminished with the help of a hemostatic. Nevertheless, due to poor control of lung lesion, the patient's KPS score declined to 40, while the patient suffered dyspnea and chest tightness even during slight activity. Hemoptysis appeared again in July 2021 and aggravated in November 2021. It would occur around 3–10 times per day, and the amount of blood was about 10–20 ml each time. The patient underwent tracheal intubation and was transferred to the Intensive Care Unit to prevent blood from eventually blocking the airway and causing suffocation. Local hemostasis by bronchoscopy, electrocoagulation with argon knife, and hemostatic were employed to ease hemoptysis. The patient was transferred to our department as hemoptysis was controlled, and after that, he suffered a fever for more than one week due to a pulmonary infection. Anti-infection and supportive care were provided, and the patient was discharged in December 2021. He returned in January 2022 due to cough, sputum, extremely and edema of both lower limbs; the KPS score was 40. The patient received only supportive care and was discharged with a resolution of symptoms. Then, the patient did not return and accept anti-tumor treatment until his death in May 2022.

3. Discussion

In the present study, we reported on the clinical efficacy of Disitamab Vedotin in treating a HER2-positive lung adenocarcinoma patient whose disease progressed after chemotherapy, anti-angiogenic therapy, and immunotherapy. Disitamab Vedotin has previously shown significant potential in HER2-positive solid cancers but has not yet been deeply applied in the area of lung cancer. The current study provides a valuable reference for the utilization of Disitamab Vedotin in HER2-positive lung adenocarcinoma.

The following factors were fully considered in the formulation of the initial therapy: advanced lung adenocarcinoma, brain metastases, and high PD-L1 TPS levels. Therefore, the first-line treatment was a combination of anti–PD-1, platinum-doublet chemotherapy, and anti-angiogenic therapy, including pembrolizumab, carboplatin plus pemetrexed, and bevacizumab. Anti–PD-1 plus platinum-doublet chemotherapy is the standard care for metastatic NSCLC patients with no oncogenic alterations. Previous studies reported PFS and updated PFS of 8.8 months and 9.0 months, respectively, in the pembrolizumab plus platinum-doublet chemotherapy group (Gadgeel et al., 2020; Gandhi et al., 2018). Although a high TPS level of PD-L1 is a predictor of improved clinical outcomes for pembrolizumab, dNLR >3 and LDH greater than the upper limit of normal were found to be correlated with worse clinical outcomes to immune checkpoint inhibitors (Mezquita et al., 2018). Therefore, bevacizumab was also adopted to ensure the efficacy of the initial treatment. Previous studies have identified that the inhibitors of vascular endothelial growth factor (VEGF) possess immunomodulatory effects (Hegde et al., 2018; Wallin et al., 2016). A combination of bevacizumab plus atezolizumab plus chemotherapy resulted in a longer PFS than either atezolizumab plus chemotherapy or bevacizumab plus chemotherapy in NSCLC patients (Socinski et al., 2018). Also, a combination of bevacizumab plus chemotherapy had better efficacy and acceptable safety in untreated nonsquamous NSCLC patients with brain metastases (Besse et al., 2015). Prior studies have noted that VEGF inhibitors prevent the development of brain metastases (Mansouri et al., 2021). Our patient had a long-term brain lesion-free, even though the lung lesions kept increasing in size, which might be ascribed to the maintenance of bevacizumab. As a result of first-line treatment and the following maintenance treatment, the PFS of our patient was 16 months. After PD to first-line treatment, the second remission of the tumor was attributed to the use of anlotinib. Anlotinib is a tyrosine kinase inhibitor, which targets receptor tyrosine kinases VEGF 1–3, EGFR, fibroblast growth factor receptor 1 to 4, platelet-derived growth factor receptor α and β, and stem cell factor receptor (Lin et al., 2018; Sun et al., 2016; Taurin et al., 2018). A phase 3 randomized clinical trial indicated that anlotinib provided prolonged overall survival and PFS in third-line treatment of NSCLC patients (Han et al., 2018). However, the efficacy of anlotinib was maintained for only some 2 months, after which the patient presented a strong resistance to all of the subsequent therapeutics until the Disitamab vedotin was administered. A significant contraction of lung and brain lesions was observed after 5 courses of Disitamab vedotin. However, as we did not examine the brain lesions during the initial administration of Disitamab Vedotin, it was impossible to assess the patient's PFS accurately.

ADC drugs represent a novel design and mechanism for anti-tumor drugs. The structure of ADC drugs usually consists of human monoclonal antibodies, linkers, and payload agents. Human monoclonal antibodies can bind to their target antigen on the surface of cells enabling it to deliver the ADC to the target tumor cell and exert an anti-tumor effect via relevant signaling pathways (Ricciuti et al., 2021). Disitamab vedotin contains an anti-HER2 antibody, which can regulate the abnormally activated signaling pathway caused by the alterations of HER2 and

further lead to apoptosis (Press et al., 1990; Vu and Claret, 2012). Antibody Disitamab is more effective than trastuzumab when targeting HER2 (Shi et al., 2022), which helps eliminate the dependence to HER2 expression level. HER2 alteration type may be one of the factors affecting the efficacy of anti-HER2 ADC. Phase II clinical trials of trastuzumab demonstrated better efficacy in NSCLC patients with HER2 mutations compared to those with HER2 overexpression (Li et al., 2018; Peters et al., 2019). This phenomenon has not been verified in Disitamab vedotin yet. Previous clinical trials suggested that HER2 IHC2+ and IHC3+ were indications for the administration of Disitamab vedotin (Deeks, 2021). The linker acts as a connection between the human monoclonal antibody and payload and is rapidly disassembled to release the payload after the ADC enters the target cell. The valine-citrulline linker of Disitamab vedotin is steady, and it is solely cleaved by cathepsins stockpiled in the lysosomes after endocytosis by tumor cells, which significantly reduces its off-target toxicity (Shi et al., 2022). Payloads function as the cytotoxic part of an ADC, which determines the mechanisms and efficacy of an ADC drug (Birrer et al., 2019). Monomethyl auristatin E (MMAE) is a peptide analog of dolastatin-10 that was identified as a tubulin inhibitor and could cause cell cycle arrest, cell death, and apoptosis. It is also the palyload of Disitamab vedotin (Bai et al., 1990; Polakis, 2016). MMAE is conjugated to Disitamab through a random coupling of cysteine, which is more homogeneous than lysine and brings out a drug antibody ratio of 4 (Shi et al., 2022). The payload can theoretically be employed to destroy additional cells in the tumor microenvironment after it has been released from the dead target cells (Ricciuti et al., 2021). Thus, the anti-tumour mechanism of Disitamab vedotin is related to targeting the HER2 signaling pathway and MMAE-induced microtubule inhibition. In vitro experiment data suggested that Disitamab vedotin may also have antibody-dependent cell--mediated cytotoxicity effects (Deeks, 2021). Our patient finally developed resistance to Disitamab vedotin, and the relevant mechanisms should be further investigated.

4. Conclusion

The current case report provides objective clinical evidence for endorsing Disitamab vedotin as a potential therapeutic drug for heavily pre-treated HER2 IHC2+ lung adenocarcinoma. Disitamab vedotin resistance was observed, so identification of the relevant mechanisms is warranted.

Declarations

Author contribution statement

All authors listed have significantly contributed to the investigation, development and writing of this article.

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Data included in article/supp. material/referenced in article.

Declaration of interest's statement

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Additional information

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