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Case Report

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Photodynamic Therapy Combined with PD-1 Inhibitor for Bronchial Tumors: One Case Report and Literature Review

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Abstract

Recent experimental studies have found that photodynamic therapy (PDT) combined with programmed death receptor 1 (PD-1)/programmed cell death-Ligand 1 (PD-L1) inhibitors can effectively inhibit in situ tumor growth and prevent tumor recurrence and metastasis, and has emerged as a new therapeutic option. However, clinical data is still limited. Here, we present a case report of a patient with advanced lung cancer who achieved complete remission (CR) after PDT combined with a PD-1 inhibitor and was free of recurrence and metastasis during 14 months of follow-up. In this way, we review the literature on PDT in combination with PD-1/PD-L1 inhibitors and provide an overview of the experimental and clinical data and possible molecular mechanisms.

Keywords: Photodynamic Therapy (PDT); Programmed Death Receptor 1 (PD-1); Bronchial Tumor; Nanotechnology-based Photodynamic Immunotherapy (PDIT); Immune Checkpoint Inhibitors (ICI).

Introduction

Metastasis and recurrence are two inevitable and thorny problems in cancer treatment. Photodynamic therapy (PDT) is considered the first-line therapy for the treatment of oligometastatic recurrent endotracheal malignancies smaller than 10 mm without extrachondral spread [1], and immunotherapy is also playing an increasingly important role, but both have their own limitations. Recent studies have shown that PDT combined with programmed death receptor 1 (PD-1) / programmed cell death-Ligand 1 (PD-L1) inhibitors performs better than single treatment modalities [2-6]. These studies are still in the laboratory stage, clinical data is still limited. Here, we report a case of a patient with advanced bronchial tumor who achieved complete remission (CR) after PDT combined with a PD-1 inhibitor and was free of recurrence and metastasis during a 14-month follow-up period.

Case report

On February 23, 2021, a 69-year-old male patient presented to our hospital with a history of cough and sputum production for more than 5 months. He had experienced hypertension for 10 years and had a 40-year history of smoking. Contrast Computed Tomography (CT) revealed a paramediastinal occupancy in the upper lobe of the right lung (Figure 1A1, A2). Considering the possibility of lung cancer and mediastinal lymph node metastasis, bronchoscopy revealed a neoplastic opening in the upper lobe of the right lung (Figure 2A), and pathology of biopsy samples confirmed squamous cell carcinoma (Figure 3). Immunohistochemistry findings were as follows: CK5/6 (+), p40 (+), ALK-D5F3 (-), ALK-D5F3-N (-), PD-L1-22C3 (TPS: -). Genetic testing was performed using amplification refractory mutation system (ARMS)-PCR, revealing no mutations in EGFR, ALK, ROS1, KRAS, or HER2. Ultra-

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sound examination, bone imaging, or cranial magnetic resonance imaging revealed no metastasis. The patient was diagnosed with squamous cell carcinoma of the right lung (cT4N2M0, stage IIIB). Bronchoscopic resection of the lesion was performed on March 15, 2021 (Figure 4 A,B), and the first cycle of chemotherapy was administered on March 17, 2021. However, the second cycle of chemotherapy was discontinued owing to elevated transaminase levels. After obtaining patient consent and excluding contraindications, the first PDT was performed on April 14, 2021 (Figure 4C). Forty-eight hours before laser illumination, hematoporphyrin (ChongQing Milelonge Biopharmaceutical Co. Ltd.) was administered intravenously at 2 mg/kg. A 3 cm diffusion segment length columnar fiber (OPTIGUIDE; Pinnacle Biologics; wavelength=630 nm) was introduced through the bronchoscope to irradiate the mucosal infiltrate of the anterior segment of the right upper lobe opening using an energy density of 150 J/cm^2 (250 mW×1200 s); the same was performed the following day. Light avoidance was strictly enforced four weeks post-surgery, and no complications occurred. Adjuvant chemotherapy was administered one-month post-PDT. Chest CT examination 2 months after PDT suggested CR (Figure 1B1,B2). However, the patient had recurrent myelosuppression after receiving the second and third cycles of postoperative chemotherapy. After comprehensive consideration and with the patient's consent, we administered maintenance therapy with sindilizumab for the patient. During the 14-month follow-up period, no tumor recurrence or metastasis was detected (Figure 1C1,C2, and 2C). The patient is currently on maintenance treatment with sindilizumab.

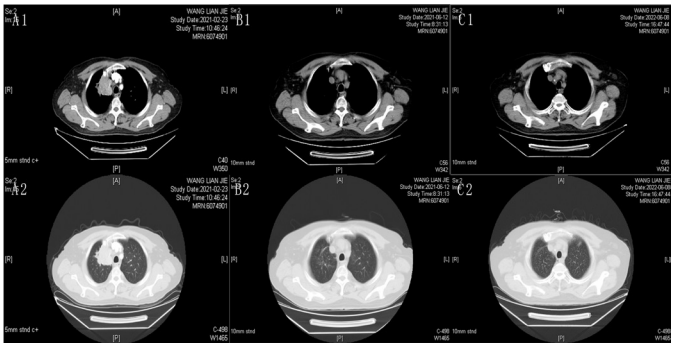

Figure 1: A1&A2, Contrast Computed Tomography images of paramediastinal occupancy in the upper lobe of the right lung. B1&B2, CT images 2 months after PDT. C1&C2, CT images after 14 months after PDT.

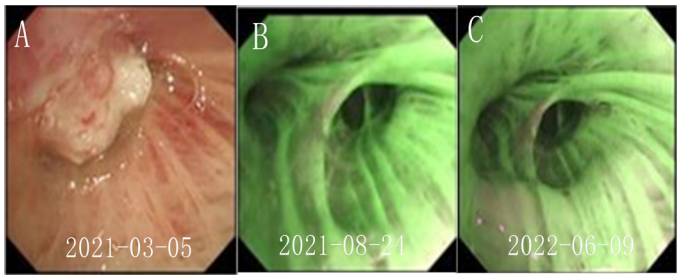

Figure 2: (A), Tracheoscopic view of mass at right upper lobar bronchus. **(B)**, Tracheoscopic view of the right upper lobe bronchus 4 months after PDT. **(C)**, Tracheoscopic view of the right upper lobe bronchus 14 months after PDT.

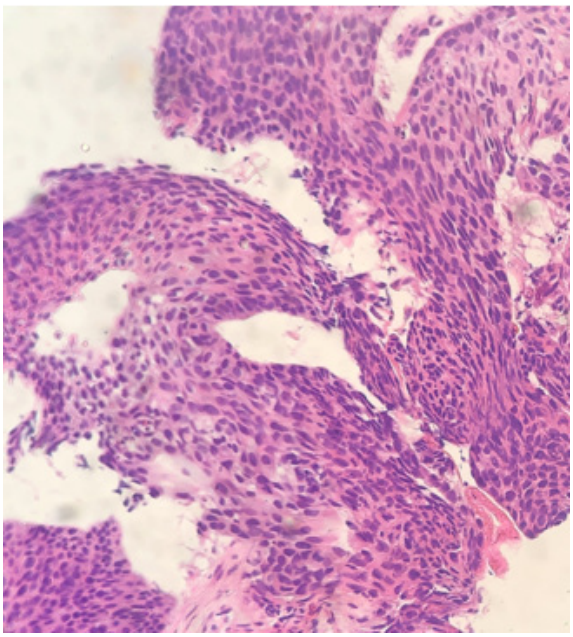

Figure 3: Pathological result was determined to be squamous cell carcinoma.

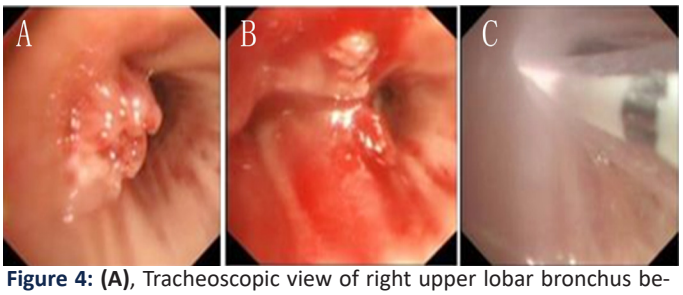

Figure 4: (A), Tracheoscopic view of right upper lobar bronchus before debridement. **(B)**, Tracheoscopic view of right upper lobar bronchus after debridement. **(C)**, Tracheoscopic view of right upper lobar bronchus during PDT at the proximal right upper lobar bronchus.

Discussion

PDT has become an important alternative treatment modality for inoperable bronchial tumors, and a large body of data demonstrates the superiority of PDT in local treatment of bronchial tumors compared to other alternative treatment modalities in terms of efficacy and side effects [7-10]. On the other hand, immunotherapy also has important clinical applications in cancer treatment. However, both therapies have their own limitations: The cytotoxic effect of PDT is limited by the spatial limitation of the photoactivation process, which limits the direct effect of PDT on the therapeutic field, while the effect of immunotherapy often fails due to the lack of immunogenicity of tumor tissue. Thus monotherapies cannot meet the current needs of cancer treatment. PDT has been shown to modulate the antitumor immune response, activate antigen-presenting cells, and reprogram the tumor microenvironment to more easily target immune checkpoints. Therefore, Immune Checkpoint Inhibitors (ICI) combined with PDT has been developed as a new therapeutic option to help enhance the antitumor immune response and improve the efficacy of preventing tumor metastasis and tumor recurrence.

PD-1/ PD-L1, as an important immune checkpoint, has been shown to be upregulated during PDT [11,12]. However, the potential mechanism remains unknown. Adjuvant IL6 produced by PDT-induced tissue damage can augment PD-1 expression through STAT3 [13] and PD-L1 expression and stability through JAK1 [14]. PDT also induces PD-L1 production by increasing T-cell infiltration and interferon (IFN)-γ expression [11,15]. In addition, PDT may cause transient hypoxia in the tumor microenvironment, which in turn potentially alters tumor and immune cell phenotypes through upregulation of PD-L1 that is dependent on HIF-1α signaling [16-18,12].

Recently, several in vivo experimental studies have shown that PDT combined with PD-1/PD-L1 checkpoint blockade is more effective than monotherapy against tumors. Bao et al. observed in an in vivo experiment that PDT targeting tumor vasculature suppressed the growth of subcutaneous 4T1 tumor and inhibited its lung metastasis, tumor PD-L1 levels were also markedly increased after PDT. In combination with an anti-PD-1/PD-L1 blockade further enhances the tumor suppression effect [11]. The enhanced permeability and retention (EPR) effect of nanoparticles allows for more selective accumulation of photosensitizers in tumor tissue, and third-generation PDT photosensitizers using nanoparticle platforms have also been studied in combined with immune checkpoint blockade. Duan et al. combined the photosensitizer with zinc pyrophosphate (ZnP@pyro) nanoparticles, which significantly inhibited in situ 4T1 tumor growth after 670 nm light activation. When combined with a PD-L1 blocker, ZnP@pyrolipPDT also prevented spontaneous lung metastasis [19]. In contrast to the conventional treatment strategy achieved by intravenous injection of anti-PD-1/PD-L1 antibodies in combination with PDT, Liu et al. assembled anti-PD-L1 antibodies and photosensitizer into nanoparticles (BDP-I-N-anti-PD-L1). Active targeting by immune checkpoint antibodies and EPR effect of nanoparticles further achieved effective accumulation of tumor tissues and eliminated MC38 mouse colon tumors by synergistic effect of PDT and ICB, generating immune memory to prevent tumor recurrence with good biosafety [20]. RGDyK as a novel PD-L1 inhibitor, Zhou et al. prepared RGDyK-modified nanoparticles (ZnPP@MSN-RGDyK). ZnPP@MSN-RGDyK nanoparticles precisely targeted β3-int to inhibit PD-L1 and showed high photodynamic treatment efficiency and excellent immunotherapeutic effects in a mouse model of NSCLC-spinal metastasis [21]. Chen et al. synthesized a nanoparticle loaded with PDT porphyrin and interfering RNA (siRNA), which combined photodynamic therapeutic ability and mediated PD-L1 gene silencing to achieve superior anti-tumor effects [22]. Wang et al. rationally designed a multifunctional micelle by integrating acid-activated cationic micelles, photosensitizers, and small siRNA. PDT or siRNA-mediated PD-L1 gene silencing with a 671-nm laser alone significantly inhibited the growth of more than 60% of B16-F10 melanomas, but the combination of the two completely inhibited tumor growth [23].

Clinical data for PDT combined with PD-1/PD-L1 checkpoint blockade therapy is scarce [6]. Wang et al. reported a patient with advanced esophageal cancer, who had been treated with two cycles of chemotherapy at the local hospital but failed. In this case, after metal stent implantation, the patient underwent a remarkable and successful treatment of PDT combined with sintilimab, a PD-1 inhibitor. An additional immune checkpoint inhibitor and chemotherapy offer the opportunity to eliminate residual and invisible tumors. The patient had an excellent prognosis that not only the primary lesion was cured, but also the metastatic lymph nodes were significantly reduced, with no tumor recurrence in the last endoscopic review [24]. Maller et al. reported a patient with squamous lung cancer (T2aN0M0) exhibiting recurrence after right upper lung lobectomy. After multiple PDT treatments, the authors found that lesions were still detectable in the tracheal ridge and proximal left main stem bronchus, and positron emission tomography (PET)-CT revealed bone metastases. Furthermore, immunohistochemical analysis of the biopsy specimens indicated that PD-1 was highly expressed. Accordingly, the authors treated the patient with intravenous pembrolizumab (200 mg every three weeks). Three months later, tracheoscopy showed CR, PET-CT revealed CR of all previously hypermetabolic areas, and no recurrence was detected during the 1-year follow-up period. This previous case report and our patient suggest that post-PDT combined with a PD-1 inhibitor could be a potential treatment strategy to increase survival benefits in patients with advanced lung cancer [25].

In April 2021, Roswell Park Cancer Institute initiated a Phase I clinical trial to evaluate the ability of PDT to amplify immunotherapy responses in patients with non-small cell lung cancer with pleural disease (NCT number: NCT04836429). Sixteen patients are expected to be enrolled. This trial evaluates the side effects of intraoperative photodynamic therapy to enhance ICI drug response. The incidence of serious adverse events (SAEs) was determined by recording the occurrence of SAEs during the first 28 days of poststudy-related immunotherapy. In addition, patients are followed over a two-year time frame for progression-free survival (PFS), overall survival (OS), immunophenotypic changes in peripheral blood CD8+ T cells, and changes in platelet-lymphocyte ratios. The study is expected to be completed in December 2023 [6].

Although many preclinical studies have shown that nanotechnology-based Photodynamic Immunotherapy (PDIT) can enhance immunity against both primary and metastatic tumors. However, the effectiveness of such nanotechnology-based PDIT has not yet been clinically validated. The safety of nanomaterials is a major challenge for the future of nanophotodynamic immunotherapy. However, cellular and animal experiments have been mainly conducted, and human experimental data are scarce. A large number of human toxicity experiments must also be performed before clinical application.

Conclusion

In conclusion, PDT combined with PD-1/PD-L1 checkpoint blockade can not only eradicate primary tumors, but also control metastatic tumors. However, there is a lack of sufficient clinical data and large-cohort studies are still needed. PDIT has the potential to move forward as a next-generation cancer treatment technology. However, human toxicity trials are needed to validate efficacy and safety before clinical application.

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