

^{131}I -chTNT injection to relieve tracheal obstruction in advanced NSCLC patient

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Abstract.

OBJECTIVE: To relieve large airway obstruction in a patient with advanced non-small cell lung cancer (NSCLC) by injecting the mouse-human chimeric monoclonal antibody radiolabeled with iodine 131 chimeric tumor necrotic treatment (^{131}I -chTNT) and to study the irradiation absorption in the tumor and critical organs.

METHODS: A 50-year-old patient with NSCLC was treated with radioimmunotherapy. His airway was still obstructed in spite of intensive chemotherapy and radiotherapy. ^{131}I -chTNT was injected into the tumor at the right bronchus through a fibroscope. A ^{131}I scan was performed during treatment, and a computed tomography (CT) scan of the chest and fibroscope were performed pre- and post-treatment. ^{131}I -chTNT distribution in tissues was followed for up to 4 weeks using gamma camera imaging.

RESULTS: The radiation material accumulated notably in the tumor, relieving the patient's symptoms by suppressing the tumor. Recanalization of the airway was achieved so that the patient was able to breathe easily and cough.

CONCLUSION: As a new type of radioimmunotherapy, ^{131}I -chTNT may be helpful in treatment of advanced lung cancer.

Keywords: Antibodies, monoclonal, radioimmunotherapy, iodine radioisotopes, NSCLC

1. Introduction

Mouse-human chimeric monoclonal antibody against single-stranded DNA directly, which is a commonly used nuclear antigen accessible to the necrotic cell within most solid tumors, such as lung cancer. The chimeric tumor necrotic treatment (chTNT) antibodies radiolabeled with ^{131}I can be injected into the necrotic core of the tumor where radiation of the radioactive nuclide (^{131}I) can destroy the tumor from inwards to outwards. Our research was to find out the distribution and local anti-tumor effect of the radioactive nuclide by intra-tumor injection of ^{131}I -chTNT through bronchofibroscopy to relieve tracheal obstruction in a patient with advanced non-small cell lung cancer (NSCLC).

2. The patient history and diagnosis

Patient A, male, 50 years old, was admitted to our department because of repeated dry cough with emphysema for 2 years and concomitant onset of asthma for 9 days. His coughing began two years ago without remarkable trigger. His cough was mostly dry, occasionally with a little white mucus but without emphysema or blood mucus. Later the patient had a small amount of emphysema and he took a chest CT

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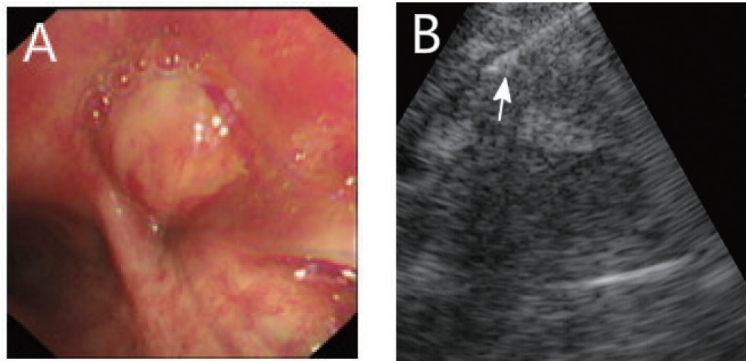


Fig. 1. The bronchofibro-ultrasonoscopy initial therapy of the 50-year-old man diagnosed with NSCLC on 15th, Aug., 2012 (A). Arrows indicate the needle sites (B).

scan in our hospital which showed a mass at the right hilum of the lung and enlarged lymph node at the mediastinum. Bronchofibroscopic biopsy showed bulging membranous part at the right main bronchus and deeply narrowed lumens. Aspiration-needle biopsy confirmed it was a squamous cell carcinoma. Considering his medical history and examination results, he was diagnosed with “right upper central lung squamous cancer (T3N2M0 IIIA)”. It was prescribed that a vinorelbine and cisplatin regimen and radiological complete remission were achieved. Because the patient refused radiotherapy and surgery due to fear, the disease relapsed locally six months later. It was prescribed gemcitabine and cisplatin chemotherapy and complete remission were again achieved. After consultation with thoracic surgeons, surgery was not performed on account of his pneumatocele and poor lung function. Instead, he was persuaded to receive chest radiotherapy, with a radiation dose of 66Gy/33F, from 1st, Nov., 2011 to 15th, Dec., 2011. Next one cycle of docetaxel was administered followed by vinorelbine plus iphosphamide, but the lymphonodes at the right lung hilum grew up remarkably. On 15th, Aug., 2012 in the nuclide ward, ¹³¹I-chTNT of 50mCi was injected via 5 points into the right main bronchus using bronchofibroscopy before his tachypnea and cough were relieved remarkably (Fig. 1).

3. Interventions and examinations

- 1) Medication. ¹³¹I-chTNT was provided by Shanghai Moln Biological Technology Limited Company. Radioaction specific activity was 370 MBq/ml, radioaction chemical purity > 95 %, immunocompetence > 50%, one injection dose of Endotoxin < 150 EU, pH value 6.5–7.5.
- 2) Usage and dosage. Three days before treatment the patient was given 10 drops of compound Iodine Oral Solution one time, 3 times a day, to block out the thyroid. The medicine was taken continuously for 10 days after treatment.
- 3) ¹³¹I-chTNT distribution in body. Anterior and posterior images of the patient were collected, using single photon emission computed tomography (SPECT) equipped with high energy collimator, at 0, 15, 24, 48, 72, 120, 168 h respectively after administration of medicines. Energy peak was 364 keV, window width 25%, matrix 1024 × 256, speed 0.2 m/s. Radiation activity in each organ was reckoned by the pairing image method according to Hammond’s description.
- 4) Chest SPECT/CT syncretizing raster display.
- 5) Bronchofibroscopy.

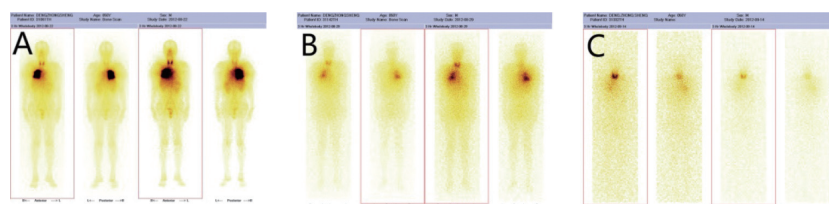


Fig. 2. ¹³¹I-chTNT Imaging 1 week after treatment (A) and 2 weeks after treatment (B) and 1 month after treatment (C) of the patient.

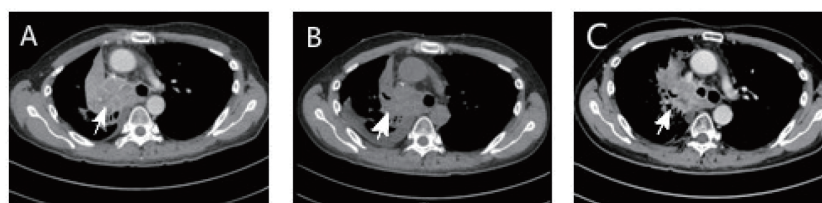


Fig. 3. Computed tomography of the chest before treatment (A) and 28 days after treatment (B) and 44 days after treatment (C) of the patient with NSCLC. Arrows indicate the tumor sites.

4. Outcomes

On 22nd, Aug., 2012 (7 days after local injection of 50mCi of ¹³¹I-chTNT), whole-body ¹³¹I (¹³¹I-chTNT) raster display and chest SPECT/CT syncretizing raster display indicated that the radioactive medicine accumulated abnormally in the right lung and the radioactivity distribution was uneven. The thyroid gland developed remarkably, with a clear profile. Liver, spleen, kidney, bladder, mediastinum blood pool, abdominal aorta, bilateral common iliac arteries and external iliac artery developed slightly, with blurred profile. Chest SPECT/CT syncretizing raster display indicated a parenchyma tumor in the right hilum of the lung with even density. The focus involved the right bronchus, and the windpipe carina inosculated with 2R and 4R lymph nodes. The right upper atelectasis was observed. The focus volume was about $7.3 \times 9.3 \times 10.0$ cm. High assembly of gout-shaped radioactive medicine accumulated highly and unevenly in the right hilum focus. Radiation accumulation in the right lower hilum of the lung was higher than that in the upper one. A small amount of pleural effusion was seen in the right thorax.

On 29th, Aug., 2012 (14 days after local injection of 50mCi of ¹³¹I-chTNT), whole-body ¹³¹I (¹³¹I-chTNT) raster display and chest SPECT/CT syncretizing raster display indicated medium accumulation of radioactive medicine in the right lung. Compared with the results 7 days ago, distribution of radioactive medicine in the tumor decreased, and the tumor volume slightly diminished. Chest SPECT/CT syncretizing raster display indicated the parenchyma tumor in the right hilum with uneven density. Low density shadow was seen. The focus infringed the right bronchus, and the windpipe carina inosculated with 2R and 4R lymph nodes. The right upper atelectasis was about $6.4 \times 7.8 \times 10.0$ cm, which is smaller compared with the former result. Medium accumulation of gout-shaped radioactive medicine was still observed in the right hilum, with fuzzy profile. A small amount of pleural effusion was seen in the right thorax.

Thirty days after local injection of 50mCi of ¹³¹I-chTNT), whole-body ¹³¹I (¹³¹I-chTNT) raster display and chest SPECT/CT syncretizing raster display were performed. The whole-body scan indicated that radiation slightly accumulated in the right lung, with a blurry profile. The thyroid gland developed remarkably with a clear profile. Chest SPECT/CT syncretizing raster display indicated that the tumor

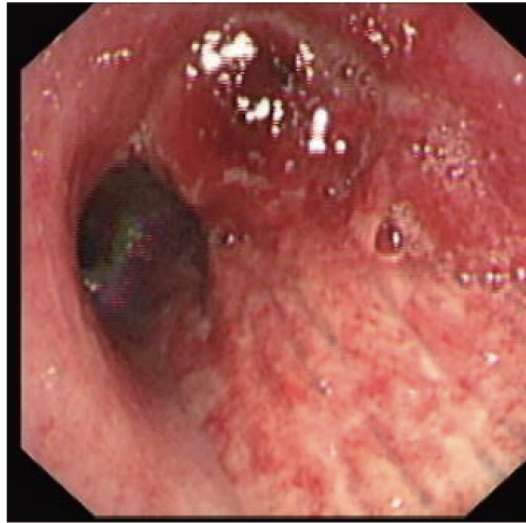


Fig. 4. The bronchofibroscopy 34 days after treatment of the 50-year-old man diagnosed with NSCLC on 18th, Sep., 2012.

inosculated with 2R and 4R lymph nodes (Fig. 2). The right upper atelectasis was observed and approximately unchanged compared with the chest CT picture on 29th, Aug., 2012 (Fig. 3). The consolidation at the right lower hilum of the lung became smaller and partly disappeared (Fig. 4). A small amount of pleural effusion was seen in the right thorax.

5. Discussion

The patient who suffered from central lung cancer in his right lung had undergone chemotherapy several times, but his tumor still progressed rapidly during the later stage of chemotherapy. The patient could no longer endure traditional chemotherapy and radiotherapy. Treatment of the bronchus by freezing or electric coagulation can only relieve the symptom of airway obstruction in a short-term but cannot inhibit the rapid growth of the tumor beneath the basilar membrane. In addition, the zone of local therapy is restricted by the large blood vessels located around the trachea. However, local intra-tumor injection of medicine can resolve the difficulties. Radioimmunotherapy (RIT) is absolutely superior to conventional chemotherapy in controlling and eliminating a local focus. Compared with the second-line chemotherapy whose efficacy is often 10% lower, local therapy may usually result in an increased control rate of local lesion, improved quality of life and enhanced tolerance of chemotherapy.

As a new type of therapy to cure cancer, RIT has developed with the monoclonal antibody technique and integrated with the radiology. RIT is to inject radiolabelled anti-tumor antibodies into the human body. When the anti-tumor antibodies combine with the tumor antigens, the radioactive nuclide is brought into the tumor to jeopardize and decay the DNA of the tumor cells by radiation, eventually leading to inhibition and necrosis of the tumor. In external radiotherapy, the dose absorbed by the irradiated tissue is 2–4 Gy/m, while that in interstitial radiotherapy is only 0.3–1.0 Gy/h. The continuing low dose of radiotherapy can make the proliferous tumor cells accumulate in the G2/M radiation-sensitive period. In addition, a great number of anoxic cells exist in the tumor tissue, the radiation-sensitivity of which is three times lower than that of normal oxygenic cells. Brachytherapy is advantageous just in

its reduced dependence on the oxygen effect. In the course of brachytherapy at a continuous low dose, reoxygenation of the hypoxic cells may increase their sensitivity to the radiotherapy.

RIT has a number of advantages such as low dose, good targeting and durative irradiation which allows more tumor cells to develop into stage G2/M to be killed. Traditional RIT usually uses the membrane antigen monoclonal antibody, but some membrane antigens do not express on all tumor cells and degradation and endocytosis of some membrane antigens may result in shedding of the antibodies bounding off the binding sites. All these will lead to failure of the treatment due to insufficiency of the radiation dose to the tumor or lack of differential targeting at the tumor in the antibodies.

Consequently, the tumor necrotic treatment antibodies have emerged. Ricke et al. in German administered CT-guided interstitial brachytherapy on lung malignancies early in 2004 [?]. They in a phase I study in 2005, also showed that the novel technique of CT-guided interstitial brachytherapy was safe for the treatment of lung tumors and yielded a very low complication rate [?]. A prospective study that treated twenty one tumors with brachytherapy under CT-fluoroscopy showed that the overall responding rate (CR + PR) for this group of patients was 71.4% [?]. The median survival time for all the patients was 10 months (95% CI: 6.6–13.4 months), with a one-year survival rate of 42.4%. Daya et al. got a similar result in India [?]. Their detailed serological analysis showed that the induced Iodine 131 chimeric tumor necrosis therapy monoclonal antibodies were mostly of the IgG1 subclass [?]. Chen et al., in Zhongshan Hospital, Fudan University, launched a pivotal study of iodine-131-radiolabelled chimeric tumor necrosis treatment in patients with advanced lung cancer. All the 107 patients enrolled in their study completed the therapy after prior failure of radiotherapy or chemotherapy for a mean of three times. The results showed an ORR of 33% in 97 non-small-cell lung cancer patients. A biodistribution study demonstrated excellent localization of the radioactivity in tumors in both systemically and intratumorally injected patients. The most obvious adverse side effect was mild and reversible bone marrow suppression [?]. Patients who received intratumoral injection of ¹³¹I-chTNT using a CT-guided catheter had a responding rate 56% [?].

The target antigen of the TNT antibody exists broadly in the karyon. It is a non-differential and nonspecific nuclear antigen. Due to denaturation of tumor and abnormally increased permeability of the necrotic cell membrane system, the TNT antibody can easily get across the cell membrane and karyotheca so as to bind with the target antigen. The ¹³¹I-chTNT injected (commercial name: Vivatuxin; national approval number: S20060061) intrudes the karyon through incomplete cell membrane of degenerative/necrotic tumor cells, and binds with the complex of target antigen DNA-histone (H1). The radioactive nuclide ¹³¹I radiolabelled on the chTNT antibody kills the vigorous tumor cells around the necrotic area, destroying the tumor from the core. ¹³¹I-chTNT is a new type of antibody that abnormally binds with the karyon in the necrotic tumor. Since most of the radioactive nuclide has bound with the target in the tumor tissue at the original position, the rest of it that may go into the blood system decreases markedly. The radiation to normal organs is thus reduced and the adverse drug reactions consequently lowered to the minimum. Therefore, local administration of target has the advantages of high efficiency and low toxicity. According to reports, the main adverse events of ¹³¹I-chTNT is temple bone marrow suppression, and almost all do not require an additional supportive treatment, as the toxicity of local injection was lower than that of intravenous administration, and no grade IV adverse events was reported in local injection. Other rare adverse events include liver, kidney, thyroid dysfunction, and fatigue, loss of appetite [?,?]. A number of reports showed that as a new type of radioactive drug in radioimmunotherapy, ¹³¹I-chTNT has a certain effect on intractable advanced lung cancers.

This is the first case in which we locally injected ¹³¹I-chTNT through bronchofibroscopy individually. It released the symptom of the patient dramatically on the next day. Fifteen days later the tumor

diminished slightly. ¹³¹I-chTNT achieved some curative effect in this case. To enhance the effect and improve quality of life, radio-chemotherapy and molecular target therapy should be combined. In the past brachytherapy, the radioactive drug was injected into the tumor only by skin puncture. In this case, multi-point injection was performed through bronchofibroscopy. This method has a benefit of locally destroying a tracheal tumor. The main adverse reaction of radioimmunotherapy is its restriction on the hematopoietic system [?,?].

Routine examination was performed for many times in this case. Blood and abnormality were not found. In addition, seven days after local injection of ¹³¹I-chTNT through bronchofibroscopy, main vessels were developed in the whole-body ¹³¹I-chTNT picture, indicating some of the medicine had directly entered the circulation system during injection. The thyroid displayed continually and increased gradually along with the radioactive intensity, which was related to the metabolism and delabelling of ¹³¹I-chTNT in the body. Blocking out the thyroid with kalium iodide was conducted based on the competitive restraining mechanism. It can restrain but cannot stop the thyroid from incepting ¹³¹I. Some patients will still have thyroiditis. Because of the above blocking out in the prophase, remarkable decline of FT3, Fr4 was not observed. Hyperthyroidism was not present in this case.

In addition, radioimmunotherapy administered simultaneously with chemotherapy is better tolerated than a course of external beam irradiation and chemotherapy [?]. This is especially beneficial for the patients who have an indication for chemotherapy but a poor performance status or other comorbidities. Percutaneous and Iodine-125 implantation and ¹³¹I-labelled antibody are mutually complementary [?], both is safe and effective regimen for unresectable lung cancer. As for adenocarcinoma, mostly originated from small bronchus and tumor location closer to the chest wall, it was limited in local through bronchofibroscopy, traditional injection by skin puncture does have some benefit to peripheral lung cancer, while the expanding of EGFR-TKI and other targeted therapy have improved outcomes dramatically in recent years. Well-designed, randomized and control study in both the laboratory and the clinic regarding this concern is needed.

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