ORIGINAL ARTICLE

A randomized study comparing the effectiveness of microwave ablation radioimmunotherapy and postoperative adjuvant chemoradiation in the treatment of non-small cell lung cancer

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Summary

Purpose: To evaluate the differences in the outcomes of patients with stage II and IIIa non-small cell lung cancer (NSCLC) treated with either ^{131}I-labeled mouse/human chimeric monoclonal antibody against intracellular DNA exposed in necrotic and degenerating regions of tumors (^{131}I-chTNT-mediated radioimmunotherapy) combined with percutaneous microwave coagulation therapy (PMCT) guided by computed tomography (CT) or with postoperative adjuvant chemoradiation.

Methods: Ninety-six patients with stage II and IIIa NSCLC were randomized into two groups. Group A included 49 patients who were treated with chemotherapy with docetaxel and cisplatin and three-dimensional conformal radiotherapy 3-4 weeks after surgery. Group B included 47 patients treated with ^{131}I-chTNT and PMCT sequentially, with follow-up chemotherapy.

Results: The survival rates of patients in group A for the first and second years were 79.59% and 48.98%, respective-

ly. The median survival was 23.0 months. Survival rates at 1 and 2 years for group B were 82.98% and 53.19%, respectively and the median survival was 29.1 months. The survival rate of group B patients for the first and second years was better compared with group A, and the difference in median survival between the groups was statistically significant (p<0.05). However, median survival and the incidence of adverse events were not significantly different between the two groups.

Conclusions: ^{131}I-chTNT radioimmunotherapy with PMCT has a complementary effect in NSCLC, which can effectively improve therapeutic ratio and survival of patients effectively and has the same effect as that of post-operative adjuvant chemoradiation.

Key words: chemotherapy, microwave ablation, non-small cell lung cancer, operative treatment, radioimmunotherapy, radiotherapy

Introduction

Lung cancer has become a cause of great concern because of increase of the environmental pollution and smoking and is a topic of hot discussions in the medical community. The most commonly diagnosed type of lung cancer is NSCLC [1-3], which accounts for 75% of all lung cancers. For patients with early stage disease (American

Joint Committee on Cancer T1, N0 NSCLC) the current treatment is lobectomy with systematic lymph node or dissection evaluation [4]. Treatment of patients with stage II and III disease is more complex. It involves surgical resection and postoperative chemotherapy and radiotherapy [5]. Unfortunately, patients with lung cancer often

Table 1. Therapies for the two groups

Group	N	Therapeutic method
Group A	49	Operation includes lobectomy (single/bilobectomy), sleeve resection or pneumonectomy with lymph node dissection + chemotherapy with docetaxel and cisplatin + three-dimensional conformal radiotherapy
Group B	47	Percutaneous microwave coagulation therapy (PMCT) + ^{131}I-labeled mouse/human chimeric monoclonal antibody (^{131}I-chTNT) + chemotherapy with docetaxel and cisplatin

have medical co-morbidities, which may preclude the option of surgical resection. In such high-risk patients, many minimally invasive and noninvasive treatment options have gained popularity. These modalities provide significant advantages, including acceptable toxicities, reduced impact on lung function, and a modest risk of post-procedure chest wall pain [6].

In recent years, microinvasive targeted therapy based on local tumor cell inactivation has provided a broad prospect for tumor treatment [7]. The idea of combining these systemic immune therapies with local ablative techniques is gaining momentum [8]. Microwaves have the ability to heat the tissue; therefore, PMCT is an effective way of treating tumors in many tissues [9,10]. However, few large-sample studies have compared the posttreatment quality of life of patients treated with PMCT and postoperative adjuvant chemoradiation.

Targeted radiotherapy using radiolabeled monoclonal antibodies has emerged as a new treatment option, especially for tumor necrosis therapy (TNT). A recent pivotal clinical trial found that patients with lung cancer are excellent candidates on whom clinical efficacy of TNT can be tested [11,12]. ^{131}I-chTNT was approved for the treatment of advanced lung cancer in China on June 13, 2003.

Our center has adopted several comprehensive treatment modalities and conducted a research study to identify a safer and more effective therapy for patients with different stages of lung cancer to improve quality of life and increase survival. The treatment currently under study is ^{131}I-labeled mouse/human chimeric monoclonal antibody (^{131}I-chTNT)-mediated radioimmunotherapy combined with PMCT guided by computed tomography (CT).

Methods

Clinical data

All patients diagnosed with biopsy-proven stage II or IIIa NSCLC between March 2008 and March 2012 were enrolled. Ninety-six patients were included, 67 men and 29 women. Their mean age was 57 years, with a range of 32 to 71 years. This study was conducted in accordance with the declaration of Helsinki and after approval from the Ethics Committee of the 303 Hospital of People's Liberation Army. Written informed consent was obtained from all participants. Thirty-eight had squamous cell carcinoma, 52 had adenocarcinoma, and 6 had adenosquamous carcinoma.

Inclusion criteria included tumor size ≤ 7 cm; no impairment of visceral organs' functionality or normal results on routine blood and liver, renal, and heart function tests; pretreatment Karnofsky performance status ≥ 70%; and no use of immune-enhancing or immune suppressive drugs 3 months before treatment initiation.

These 96 patients were randomly divided into two groups: group A: 49 patients receiving chemotherapy with docetaxel and cisplatin as well as three-dimensional conformal radiotherapy 3 to 4 weeks after surgical treatment; and group B: 47 patients treated with ^{131}I-chTNT-mediated radioimmunotherapy and PMCT sequentially, followed by chemotherapy with docetaxel.

Treatment modalities

The treatments administered to the patients are summarized in Table 1.

Group A:

Surgery: Lobectomy (single/dual), sleeve resection, or pneumonectomy, including lymph node dissection.

Chemotherapy: Chemotherapy was initiated 3 to 4 weeks after the operation with docetaxel 135 mg/m^2 day 1 and cisplatin 75 mg/m^2 day 1 and repeated every 21 days.

Radiotherapy: Radiotherapy was initiated 4 weeks after the operation or in the second chemotherapy cycle. Linear accelerator was used to irradiate the hilar region, mediastinum, and the upper side of the two clavicles. Three-dimensional conformal radiotherapy was used to deliver a total dose of 40-60 Gy , according to the patients' tolerance. For most patients, around 20 Gy a day were delivered 5 times a week.

Group B:

Percutaneous microwave coagulation therapy:

10 mg valium were injected intramuscularly before

the operation. The tumor location, number of nodes, tumor size, and blood flow features were identified by imaging. The body position of the patient was adjusted after selecting the puncture route and the positioning point on the body's surface. The puncture route should be such as to avoid the nerves, main bronchus, pericardium, and aorta. The conformal paracentesis area was sterilized, numbed locally, and incised (2 mm) with a sharp knife. CT images were used to identify the selected puncture route for the tumor puncture, and then the microwave antenna was implanted for solidification treatment. An intravenous injection of 100-200 mg propofol was administered if required. The power was 40-70 W and the response time on each point was 180-1500 s. Microwave treatment was performed using the strong echo scattered from the radiating antenna center to the outside. The solidification treatment was implemented with different methods according to the tumor size and shape, signal distribution, and blood flow direction. The goal was to include 0.5 cm of the lateral tissue around the tumor in the ablation range in order to form "a safe edge" and kill all the tumor cells.

^{131}I-chTNT local dosing therapy:

The iodine compound was mixed with the patients' food 3 days in advance, and thereby administered orally 10 drops per dose, three times a day until 1 week before the treatment ended. The selected paracentesis area was sterilized. Through the ablation needle 18.5-37 MBq/cm^3 (0.51 mCi/cm^3) ^{131}I-chTNT per dose were injected, with a maximum total dose per tumor of 1850 MBq (50 mCi). The drug injector was connected to the puncture needle without seal under imaging guidance (CT, X-ray, or digital subtraction angiography) to inject the drug into the center of the tumor. The ^{131}I-chTNT was manufactured by Vivatuxin, an atomic high-tech isotope pharmaceutical company in China. This preparation measures 0.8 mm×4.5 mm and has a titanium alloy cover. Its half-life is 59.6 d and its energy is 27.4-31.5 keV X-ray and 35.5 keV γ-ray. The activity of the particles is 0.5-0.6 mCi and the prescribed dose is 160 Gy and it is sterilized using high temperatures.

Follow-up chemotherapy

Docetaxel 135 mg/m^2 day 1 and cisplatin 75 mg/m^2 day 1, repeated after 21 days.

Follow after treatment

The tumor volume was evaluated according to WHO criteria [14] and compared between the two groups. A hemogram and repeat CTs were performed 1, 3 and 6 months after treatment to evaluate the local treatment effect. The patients were followed up for 59 months after treatment.

Evaluation criteria

1) The treatment efficacy was evaluated objectively according to tumor pathologic classification and response criteria according to World Health Organization (WHO). Complete remission (CR) was defined as complete disappearance of the tumor i.e. the tumor is either not visible or it appears as a cord-like structure on imaging. Partial remission (PR) was defined as a reduction in tumor size by >50% of that before treatment. No change (NC) was defined as reduction of <50% or an increase of <25% in the tumor size. Progressive disease (PD) was defined as an increase of >25% in tumor size

Table 2. Comparison of clinicopathological data of patients with NSCLC in two groups

Clinicopathological data	Group A N (%)	Group B N (%)	x^2	p value
Sex			0.01	>0.05
Male	34 (69.39)	33 (70.21)		
Female	15 (30.61)	14 (29.79)		
Age (years)			1.46	>0.05
<60	30 (61.22)	23 (48.94)		
≥60	19 (38.78)	24 (51.06)		
Length (cm)			0.21	>0.05
<5	21 (42.86)	18 (38.30)		
≥5	28 (57.14)	29 (61.70)		
Pathological types			0.24	>0.05
Squamous cell carcinoma	18 (36.73)	20 (42.55)		
Adencarcinoma	27 (55.10)	25 (53.19)		
Adenosquamous carcinoma	4 (8.16)	2 (4.26)		
Stage			0.00	>0.05
II	19 (38.78)	18 (38.3)		
IIIa	30 (61.22)	29 (61.70)		

compared to that before the start of treatment or the development of a new lesion(s). 2) According to recent therapy evaluation standards CR and PR are regarded as indicators of effective treatment. The treatment efficiency after 6 months is calculated by adding together patients with a CR, PR or NC (extended control rate).

The randomly selected patients were followed up after 6 months to assess and compare the survival rates and quality of life of the two groups after 1 and 2 years of treatment. 3) Evaluation of adverse events was done to determine hematological or non-hematological as per WHO classification for adverse events of anticancer drugs.

Statistics

SPSS 11.5 statistical package (SPSS Inc., Chicago, Ill) was used to perform the statistical analyses. Continuous data were expressed as mean ± standard deviation. For detailed analysis ANOVA and Pearson's correlation test were used. Two-tailed $p<0.05$ was considered to indicate statistical significance.

Results

Comparison of clinicopathological data

No significant differences were noticed between the groups (Table 2).

Short-term treatment efficacy

Group A: CR and PR after 1, 3, and 6 months were 57.14, 63.27, and 65.31%, respectively. The extended control rate after 6 months was 69.39%. Group B: CR and PR after 1, 3, and 6 months were 51.06, 70.21, and 80.85%, respectively. CR+PR+ NC after 6 months was 87.23%. The extended control rate after 6 months was significantly better in group B than in group A ($p<0.05$, Table 3).

Long-term treatment efficacy

All patients were followed up from 11 to 59 months (median 38.7). The visiting rate was 91.2%. Ninety percent of the patients experiencing metastasis did so in the first 2 years after treatment. Forty-five patients developed metastatic disease, attributed as follows: 15 patients experienced metastasis in the lymph nodes, 13 in the lung and pleura, 9 in the brain, 6 in the bone, and 2 in the liver. There was no significant difference in the number of metastatic cases between the groups ($p>0.05$).

The survival rates at 1 and 2 years for group A were 79.59% and 48.98% respectively, with median survival time 23.0 months (range 12.1-48.6). The survival rates at 1 and 2 years for group B were 82.98 and 53.19% respectively, with median survival 29.1 months (range 16.7-59.2). The median survival in group B was significantly better than that in group A ($p<0.05$); however, the survival rates were not ($p>0.05$).

Adverse events

Myelotoxicity in group B was seen in 9/47 patients (14.89%), higher than that in group A (4/49, 8.16%) but without statistical significance; Radioactive esophagitis in group A was seen in 10/49 patients (20.4%), significantly higher than than in group B (2/47, 4.25%; $p<0.05$). No obvious differences were noticed in gastrointestinal tract adverse events, neurotoxicity, liver and renal function impairment, or radioactive pneumonia between the two groups. The adverse events generally subsided after appropriate treatment without causing mortality.

Discussion

The 5-year overall survival of patients with stage II and IIIa NSCLC ranges between 12 and 29.8%, suggesting the need for more radical operative approaches in order to improve the long-term survival and the therapeutic ratio [14].

Large-sample sized clinical researches in stage III patients indicate that postoperative adjuvant radiotherapy and chemotherapy can achieve beneficial results [15,16]. The main purpose of postoperative adjuvant radiotherapy and chemo-

Table 3. Efficacy and local control in the two groups of patients

Grouping	Total efficacy (CR+PR)			Extended control (CR+PR+NC)
	1 month N (%)	3 months N (%)	6 months N (%)	
Group A (N=49)	28 (57.14)	31 (63.27)	32 (65.31)	34 (69.39)
Group B (N=47)	24 (51.06)	33 (70.21)	38 (80.85)	41 (87.23)
x^2	0.36	0.52	2.94	4.47
p value	>0.05	>0.05	>0.05	<0.05

CR: complete response, PR: partial response, NC: no change

therapy is to eliminate residual tumor cells and subclinical pathology after surgery, to improve the extended control rate and reduce the postoperative recurrence rate.

The experimental results of a study conducted by Girard et al. [17] indicated that for patients with resectable stage III tumors treated with different regimens of induction chemo-radiotherapy, the overall median, 1-year and 3-year survival rates were 87%, and 43%, respectively. These results indicate that a therapeutic strategy combining local and systemic treatment is highly feasible.

With the outstanding development of scientific technology and new medical devices in recent years, new treatment methods are being developed constantly, especially micro-invasive targeted treatments based on partial inactivation of tumor cells. This method has become one of the effective therapies for comprehensive tumor treatment in modern times [18].

Some authors believe that ^{131}I-chTNT application after surgery improves treatment efficacy [19]. As thermal ablation therapy that has a direct effect on tumor tissues, PMCT is an effective way to target a larger tumor area [20,21]. Heating by microwaves [22] can lead to solidification and necrosis of tumor tissues, and the cell structure and function undergo a number of lethal changes, including abnormal permeability of the cell and nuclear membranes, scattering and gathering of chromosomes, deconstruction of double-stranded (DS)-DNA, and appearance of degenerated single-stranded (SS)-DNA.

These changes enable macromolecular ^{131}I-chTNT to enter the nucleus through the incomplete membrane of degenerated necrotic tumor cells and connect with the targeted SS-DNA compounds. Any living tumor cells around the necrotic area will be killed by the radioactive rays emitted by ^{131}I-chTNT [23,24].

Experimental results from Anderson et al. [25] indicate that the treatment efficacy of ^{131}I-chTNT increases after ablation treatment. This indicates that radiofrequency ablation for the treatment of metastatic liver cancer before ^{131}I-chTNT administration can significantly increase the ^{131}I-chTNT uptake of tumor necrotic tissue so as to improve the therapeutic effect.

Similarly, for patients with lung cancer, if the ^{131}I-chTNT radioimmunotherapy is implemented after the microwave ablation, this can increase the effectiveness of the microwave ablation and also enhance the effectiveness of the ^{131}I-chTNT radioimmunotherapy. This approach can lead to improved therapeutic results in patients with larger tumors.

During this study, it was observed that the tumor volume had slightly increased on review CT 1 month after treatment in group B. This may appear like progression, however this increase might be due to the fact that the tumor tissues swell up after the microwave ablation and the hot solidification range extends up to about 1.5 cm from the tumor edge [26].

After microwave ablation it is necessary to implement a supplementary treatment for undamaged and residual tumor "insulae" in order to minimize the incidence of recurrence and metastasis.

The results of our study are similar to those obtained by Kodama et al. [27], suggesting that cytoreductive surgery may have a potential role in local control as an adjuvant treatment for patients with NSCLC.

We also observed that there were no obvious differences in survival between the groups at 1 and 2 years; however, the median survival time in group B was better than that in group A. This implies that treatment with ^{131}I-chTNT-mediated radioimmunotherapy and PMCT sequentially, followed by adjuvant chemotherapy has a good effect in stage II and IIIa NSCLC patients, with a marked improvement in the extended control rate. This treatment improved the therapeutic ratio and alleviated the clinical symptoms in patients as effectively as postoperative radiotherapy and chemotherapy.

This therapy has some advantages such as being microinvasive, having wide indications, and being a repeatable treatment. It is one of the effective, comprehensive therapies and plays an important role in clinical applications [28] and deserves promotion. The researchers of the present study will continue to visit patients at random to determine the 5-year survival rate in order to provide a more long-term, objective and accurate assessment of the treatment effectiveness [29-31].

Acknowledgement

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