Clinical Study of Radioimmunotherapy of Tumor with Multiple Low-dose ^{188}Re-CL58 and High dose ^{131}I-chTNT

Yong Ding[1], Jiahe Tian[1], Wuwei Yang[2], Zhi Yang[3]
Faliang Xu[2], Shuwen Zhang[1], Yinmao Chen[1], Zhiwei Guan[1]

[1] Department of Nucl. medicine, The General Hospital of PLA, Beijing, 100853
[2] The Military Medical Academy 307 hospital, Beijing, 100850
[3] Oncology Hospital of Beijing University, 100036

Abstract **Objective** To compare the efficiency and toxication of radioimmunotherapy(RIT) with multiple low-dose (MLD) ^{188}Re-CL58 and high dose (HD)^{131}I-chTNT on treatment of cancer. **Methods** Patients were treated with MLD of ^{188}Re-CL58 (or ^{131}I-Hab18) or HD of ^{131}I-chTNT. The imaging technique of FDG-PET and the observation of tumor specific markers in blood were need to appraise the efficiencies of the radioimmu-notherapy. **Results** After treatment with MLD-RIT and HD-RIT, FDG accumulation in lesions was decreased significantly. Compared with larger lesions. In some cases, SUV of the micro-metastases were even brought down to the normal line. After treatment with RIT, tumor markers such as CEA also decreased in varying degree, with MLD ^{188}Re-CL58 more efficient than HD ^{131}I-chTNT. MLD ^{188}Re-CL58 affected the immune system positively for it brought down CD_3^+ cell and brought up the ratio of CD_4^+/CD_8^+. MLD RIT induced no visible blood toxication. Both of them had no toxic effect on liver and kidney. **Conclusion** MLD RIT were efficient for the treatment of micro-metastasis. MLD RIT partially relief the immune system from suppression, The toxication of RIT was manifested mainly as blood cell inhibition.

Key Word Positron emission tomography (PET); monoclonal antiboby; Cancer; Radioimmunotherapy;

As our previous animal studies had proved that low dose ionizing irradiation enhanced antitumor immunity, low dose radioimmunotherapy(RIT) possessed the same potential of immunity enhancement[1,2]. Our previos studies also showed that low dose RIT induced tumor cells to apoptose and senescence[3]. Encouraged by the promising results of low dose RIT to effectively inhibit tumor growth in mice, we adopted low dose ^{188}Re-CL58 in an clinical therapeutic experiment in order to evaluate its potency in metastatic tumor therapy.

MATERIAL AND METHODS

Antibody labeling and therapy protocol

The patients were divided into two groups. One group underwent multiple low dose therapy protocol with CL58, a subtype antibody against CEA, the other underwent single large dose therapy protocol with chTNT, a combined antibody against nuclear antigen. For CL58 (provided by clinical oncology institute of Beijing university, immune activity > 85%) labeling, ^{188}Re was first added in solutions contained GH, Tartaric Acid, $SnCl_2$, then CL58, hydrogenated by 2-thioethyol, was mixed into it, reaction 1.5 hours at room temperature for labeling. Labeling rated was detected with thin-layer chromatography -paper electrophoresis method. If labeling rate was less than 95%, the labeded antibody was purified with Sephadex G50. chTNT was labeled with ^{131}I, provided by Shanghai Huachen biological company. For the multiple low dose therapy group, 188Re- CL58 (^{131}I-HA18 for hepatic cell carcinoma) was admitted every the third day up to 5 times, the dosage each time 0.35mCi/Kg. For the single large dose group, ^{131}I-chTNT was admitted once for all, with a dosage of 1mg/mCi.

Patients demography

All patients included were positively dignosed as suffering from metastatic tumors, with an expectation life of more than 3 months and without any therapy in the last 4 months. Blood tests showed

Correspondence to: Yong DING, PhD Department of Nuclear medicine, The General Hospital of PLA, Beijing 100853, China.
Tel: 010–66939424. Email: dingyong301@csnm.com.cn.
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normal hepatic and renal function as well as normal peripheral WBC and platelet counts (WBC > 3000/mm^3, platelet>80000/mm^3). Before admission, all patients agreed with the protocol. Totally, 23 patients were included, 14 in the multiple low dose group (7 male, 7 female, ages ranging from 31 to 71 years old, with a median age of 57), and 9 in the single large dose group (5 male, 4 female, ages ranging 18~64 years old, with a median age of 48). The pathological demography of the two groups were as the followings: 6 cases were small cell lung cancer, 3 colon carcinoma, 3 esophageal carcinoma and 2 hepatic cell carcinoma in the multiple low dose group; 5 cases were small cell lang cancer, 1 esophageal carcinoma, 1 gallbladder carcinoma, 1 cerebral glioma, and 1 fibrosarcoma in the single large dose group.

^{18}F-FDG whole body scan

Before scanning all patients were fasted at least 4 hours. ^{18}F-FDG (10-15 mCi or 0.15mCi/Kg) was injected in venous and whole body scanning was started 45~50 minutes after with ECAT EXACT HR +PET from SIEMENS. Routinely, the scan length was 5~6 beds, scan speed 10min/bed and transmission time 3.5 min/bed. Image reconstruction was progressed with OSEM method and SUV(standard uptake value) was calculated with ROI method. ^{18}F-FDG scan was ensured to carry out under same conditions before and after therapy.

Statistics

We compared the SUVs before and after multiple low dose RIT with t test, and make the statistic analyses to the CEA plasma levels between the two therapy groups with mann-whitney test and toxication with ANOVA analysis.

RESULTS

Therapy results

For the multiple low dose group treated with ^{188}Re-CL58, SUVs of tumor decreased dramatically after the treatment in ten cases, some of which even became normal; the CEA plasma level also decreased in all cases. For the single large dose group treated with ^{131}I-chTNT, the CEA level of three cases among the five with elevated level of CEA, decreased, while the CEA level of the other two increased. The results of mann-whitney test for CEA level changes of the two groups suggested that multiple low dose of ^{188}Re - CL58 was more efficient than single large dose of ^{131}I - chTNT in tumor control (Fig.1, 2).

Subgroups of lymph cells in peripheral blood

For all patients in this study, venous blood was drawed before and after treatment to detect CD_3^+, CD_4^+ and CD_8^+ with ELISA method. For the multiple low dose group, the count of CD_4^+ increased and CD_8^+ deceased, resulting in the increase of CD_4^+/CD_8^+. For the single large dose group, the count of CD_4^+ decreased and CD_8^+ inceased, resulting in the decrease of CD_4^+/CD_8^+. (table1)

Toxication and complication

During and after the treatment, no complications of fever, sickness, nausea, etc, occurred. Blood tests showed no damage to hepatic and renal function. Before and after treatment (1 day, 3 days, 5 days, 7 days, 2 weeks, 4 weeks after treatment), peripheral blood cell tests showed that hemoglobulin, platelet and WBC counts declined dramastically after the treatment of large dose of ^{131}I-chTNT ($P < 0.05$), while no significant changes after the treatment of multiple low dose of ^{188}Re- CL58 (Fig3, 4, 5).

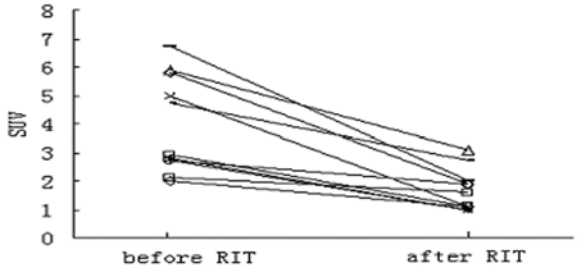

Fig.1 The Change of Tumor´SUVs treated with ^{188}Re–CL58

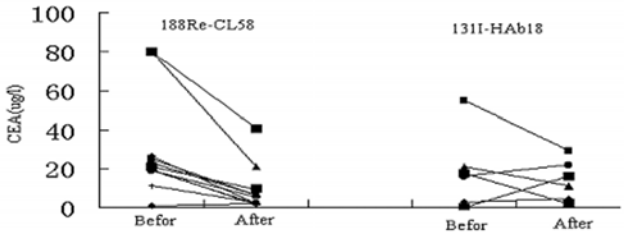

Fig.2 The Change of CEA plasma level treated with ^{188}Re-CL58 and ^{131}I-HAB18

Table 1. Variations of T lymph cells treated with ^{188}Re-CL58

Group	n	CD3+	CD4+	CD8+	CD4+/CD8+
Normal		60.0±3.5	47.0±3.6	27.0±2.6	1.7±0.5
Before RIT	23	55.3±4.4	37.2±3.1	34.6±2.9	1.1±0.5
^{188}Re-CL58	14	53.7±3.6	45.9±3.2*	28.2±2.6*	1.6±0.5*
^{131}I-chTNT	9	35.7±3.8*	21.6±3.2*	57.9±3.1*	0.6±0.6*

* P<0.05

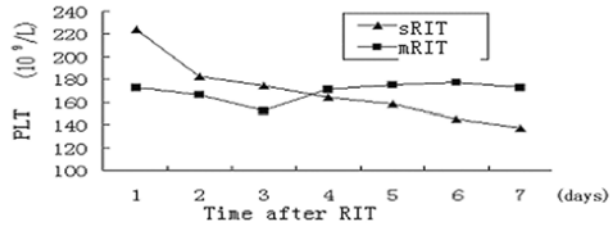

Fig. 3 Variations of PLT treated with sRIT and mRIT

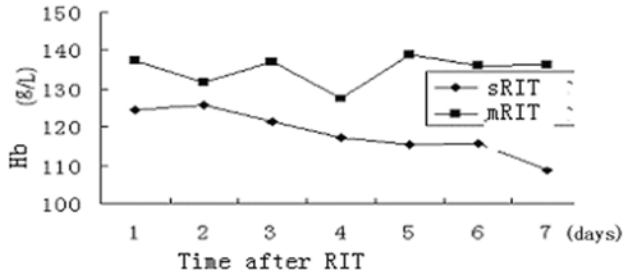

Fig. 4 Variations of Hb treated with sRIT and mRIT

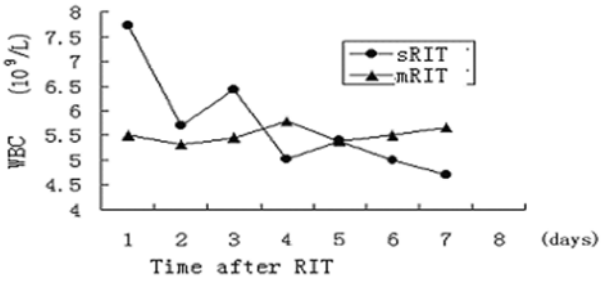

Fig. 5 Variations of WBC treated with sRIT and mRIT

DISCUSSION

^{18}F-FDG-PET is a kind of molecular level of imaging technique, with ^{18}F labeled deoxyglucose, an analogue of glucose, as tracer agent. Usually, tumor cells expressed and synthesized more glucose transporter, such as Gult 1 and Glut 3. At the same time the expression of hexokinase in tumor cells is up-regulated and phosphatase down-regulated. As a result, more FDG is uptaken and then accumulated in tumor cells than in nomal cells[4]. So tumors are usually imaged as hot spots[5]. The uptake of FDG by tumor cells can be quantified by SUV (standard uptake value). With quantification as well as quality methods, FDG-PET, as many studies have proved [6], could accurately evaluate the efficiency of treatment[7,8]. In our study, FDG-PET scan one month after ^{188}Re-CL58 treatment showed less FDG accumulationin and smaller SUV in tumor sites than that before the treatment in all cases of the multiple low dose group. For smaller lesions, the decrease of SUV were even more dramastic, perhaps due to their richer blood supply and then more radiolabeled antibody uptaken compared with larger ones[9]. That is why we focused on metastatic leions of small size to carry out the therapy[10].

Tumor specific antigens circulating in blood, such as CEA, AFP, CA125, etc, are also used to evaluate the efficiency of therapy [11]. For multiple low dose group, the plasma level of such tumor specific antigens as CEA and AFP decreased in the same way as SUV did in all cases, which further proved the efficiency of this kind of therapy. On the contrary, the treatment of single large dose of ^{131}I-chTNT was not so efficient as multiple low dose of ^{188}Re-CL58 treatment. In this group, the CEA level of 2 cases became even higher after the treatment, suggesting less efficiency of this kind of treatment. Like other kinds of tumor therapy, RIT has its own toxication, and hemopoietic inhibition, which is detected as blood cell counts declination, is the main kind[12,13]. That is why hemopoietic toxication decides on the largest dosage of radiolabed antibody for admission. Our study suggested that multiple low dose of ^{188}Re-CL58 had less hemopoietic inhibition than single large dose of ^{131}I-chTNT.

Anti-tumor immune mainly consists of cell immune, in which T lymph cells are playing a central role. For patients who suffer from tumors, their T lymph cell counts often decrease and ratios between the functional subgroups are misplaced. The immunity of the patients are under a condition of suppression. Besides, the neccesiated radiotherapy and chemotherapy make the immunity suppression even worse. But our study showed that multiple low dose of ^{188}Re-CL58 in an extent amended the immunity suppression as after the treatment CD_4^+ counts increased and CD_8^+ counts decreased, resulting in up-regulation of CD_4^+/CD_8^+. So we would say that this kind of treatment possessed a potency of immune excitement, just as low dose ionzing irradiation did, which had been reported by other researchers[14]. As for single large dose of ^{131}I- chTNT treatment, no such immunity exciting effect were achieved. It may deteriorate the immunity suppression on the contrary.

In conclusion, according to our study, multiple low dose of ^{188}Re-CL58 could efficiently treat metastatic lesions of small sizes, the efficiency of which was better than that of single large dose of ^{131}I-chTNT. Multiple low dose of ^{188}Re-CL58 possessed the potency of immunity excitement and no severe hemopoietic inhibition effect.

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