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Dosimetry of chimeric TNT in lung tumor patients

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Abstract The purpose of this study was to assess the absorbed dose of tumor and main critical organs in ^{131}I labeled chimeric tumor necrotic treatment (chTNT). In 9 patients, a single intravenous dose of (29.6±3.7) MBq/kg was administered. Blood samples were drawn at different time intervals, and urine was collected for up to one week. Tissue distribution of ^{131}I –chTNT was followed for up to one week by gamma camera imaging. Absorbed doses to the whole body and to normal organs were computed according to the MIRD scheme using Mirdose-3 software. S-factors for lung tumors were estimated by comparison with lungs of similar mass and position in the body. It was found that mean serum disappearance half time values for ^{131}I-chTNT were (4.93±9.36) h and (61.7±21.2) h for α, β respectively, while that for whole body was(99±10) h. Mean urine biological clearance half time value was (90±10) h. The absorbed dose to tumor was (8.28±2.65) Gy, and the tumor-to-nontumor dose ratio was 3.95±1.55. And the mean effective dose to patients was (1.02±0.29) mSv/MBq.

Key words Radioimmunotherapy, Radiation dosage, Iodine radioisotopes

CLC numbers R817.5, R734.2

1 Introduction

The mouse-human chimeric monoclonal antibody (chTNT) may be applicable to the majority of human solid tumors, such as lung cancer, colon carcinoma, and prostate cancer, as has been confirmed by many studies [1-3]. As a new drug, the phase II trials of ^{131}I-chTNT were completed at Zhongshan Hospital. In this paper, we report the methods for measurement of ^{131}I radioactivity and dose estimation for attempted dosimetry predictions about tumor and critical organs.

2 Methods

2.1 Patients

The pilot study involved nine lung tumor patients, including four patients with bronchogenic carcinoma, two with mammary cancer, and one each with synovial sarcoma, periosteal sarcoma or rectum carcinoma. All patients had the Eastern Cooperative Oncology Group Performance Status Scale (ECOG PS) 2. None of them had any exposure to murine antibody before, nor was negative in human antimouse antibody test and sensitive to iodine. Thorax CT scan was carried out prior to the therapy. All patients gave written informed consent for their participation.

Remark on the patients: female 3 and male 6, in ages of 18-74 with the median at 45.6, and in weight of (49.6±6.5) kg.

2.2 Drug and machine

Specific activity of the ^{131}I-chTNT was 370MBq/mL, in 95% of radiochemical purity and 50% of immunoreactivity. The drug was supplied by Shanghai MediPharm Biotech Co, Ltd. Dose activities were measured in a CRC-15R calibrator (Capintec Inc NJ, USA). The radioactivity of blood and urine sam-

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ples was measured in a FMJ-182 γ counter (Rihuan Instrument Factory of Shanghai). Whole body images were recorded with a Marconi IRIX Ⅲ digital gamma camera equipped with a high energy parallel collimator.

2.3 Pharmacokinetics

2.3.1 Administration

Each patient was given ten drops of saturated potassium iodine (SSKI) solution orally t.i.d (three times per day) three days before (29.6±3.7) MBq/kg of ^{131}I-chTNT was administrated intravenously and until ten days after administration [4].

2.3.2 Counting of samples

About 1 mL blood was drawn in heparinized vaccutainer tube through a catheter installed in a vein contralateral to the injection site. Blood samples were collected at 5 min and 1, 2, 4, 6, 24, 48, 72 and 168 h after injection. In 30 min after sampling, the plasma was separated from the cellular material by 15 min centrifugation at 4000 r·min^{-1} in a microcentrifuge.

After administration of the ^{131}I-chTNT, urine samples were collected on a daily basis for seven days.

Specific activities of the plasma and urine samples of known volumes were obtained by comparing their counts to measurement of a standard source.

2.3.3 Imaging

The ^{131}I-chTNT was administrated intravenously to the patient on the imaging table. The data acquisition was done with the camera windows, opened at 25%, being adjusted on the 364keV photoelectric peak of ^{131}I. Whole-body scanning was done at a rate of 20cm/min in a constant camera-to-patient distance. Anterior and posterior whole-body imaging was performed at 0.5, 24, 48, 72, 120 and 168 h after the ^{131}I-chTNT administration. Geometric mean of the anterior and posterior counts was obtained from selected regions of interest (ROIs) to determine radioactivity within the whole body, brain, lungs, heart, liver, spleen, kidneys and tumor [5-7]. Thyroid counts were obtained from anterior images only. A background region was taken below the thyroid gland to subtract underlying activity in the neck blood vessels.

2.3.4 Dead time correction

Dead-time correction factor of the gamma camera was obtained with a paralyzable model[8]:

$$N'=Ne^{-Nv} \quad (1)$$

where v is the dead-time constant, N' is the observed count rate, and N is the true count rate.

And the dead-time correction factor C_p is

$$C_p = N/N' = e^{Nv} = e^{N'vC_p} \quad (2)$$

2.3.5 Detection efficiency

The standard source was made by introducing 8.44 MBq ^{131}I onto a 3cm×4cm silica-gel- impregnated glass-fiber sheet and sealing it with tape. It was counted to 10^6 counts for three times by the camera placed in the same geometry as above to calculate the average count rate and detection efficiency.

2.4 Dosimetry

2.4.1 Biodistribution

The time-activity curves for the whole body, selected organs and tumor were obtained from the scintigraphic images by tracing regions of interest around them. The geometric mean of the anterior and posterior view for each ROI was used to calculate the percent injected dose (%ID). The geometric mean of the counts in the whole body scintigram at 0.5 h after injection was corrected for radioactive decay from the time of injection, and this value was taken as 100%ID[9].

2.4.2 Dosimetry calculations

The method developed by the Medical Internal Radiation Dose (MIRD) Committee[10] was used for dosimetry calculation. We calculated the mean absorbed dose of normal organs by Mirdose 3.0 software (Internal Dose Information Center at Oak Ridge Institute for Science and Education, Oak Ridge, TN), using the dynamic bladder model (4h VOID) [9,11,12].

We summed up the resident time of lungs and tumor as the “lungs”. Corrections were made for lungs masses. For mass of the tumor tissue (m_T) we assumed unit density and employed the CT volume (V_T)[13] :

$$m_T=1\times V_T \quad (3)$$

This approximation should be satisfactory as their tumor volume could not change rapidly during this study. Tumor background subtraction was attempted using CT scans to estimate true background thickness [6]. Absorbed doses to tumor tissues (D_T) were estimated using the same approach taken for normal organs [6]. S-factors for lung tumors were estimated by

comparison with lungs. According to that,

$$D_T/\tau_T = D_{lungs}/\tau_{lungs} \quad (4)$$

$$D_T = m_{lungs} \times (D_{\text{“lungs”}} - D_{lungs})/m_T \quad (5)$$

where D_{lungs} and $D_{\text{“lungs”}}$ are the mean absorbed dose to lungs, “lungs”, respectively, τ_T and τ_{lungs} is the residence time in tumor, lungs, respectively.

3 Results

The detection efficiency of gamma camera was $(41.7\pm1.7)\cdot s^{-1}\cdot MBq^{-1}$, the dead-time constant v was (3.7±1.0)μs, and the dead-time correction factor was less than 1.039.

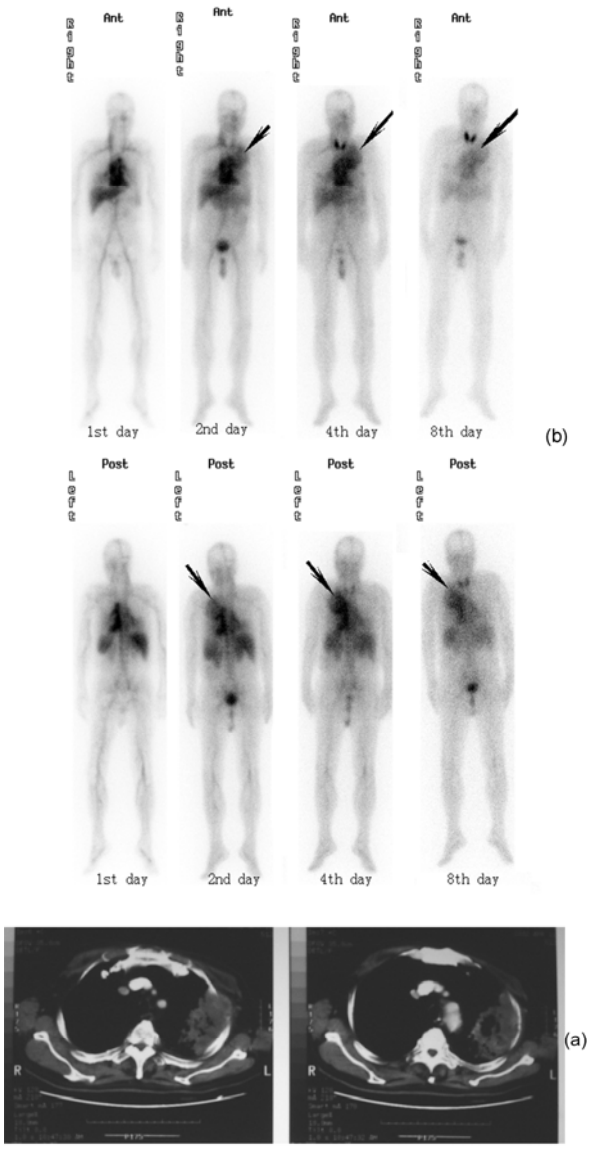

Fig.1 No.5 patient’s thorax CT scan (a) showed the tumor (maximum dimension 7cm) located in upper lobe of left lung involved left chest with cavity having irregular margin thick walls. ^{131}I-chTNT whole body scan (b) showed the tumor be visualized at 2d (see arrow), and noted at 4d.

Serum clearance follows a two-exponential model. Mean serum disappearance half time values for ^{131}I-chTNT were (4.93±9.36) h and (61.7±21.2) h for α, β, respectively. Mean urine biological clearance half time value was (90±10)h. As blood pool activity in the whole body, liver, lungs, and spleen decreased, tumor and thyroid activity became more prominent (Fig.1). Activity clearance of whole body and some primary organs’ follows a one-exponential model. The mean disappearance half time values are listed in Table 1. Mean thyroid effective uptake half time was (55±18)h.

Table 1 The ^{131}I-chTNT clearance half-times of the whole-body and critical organs

Organs	$T_{1/2}$ /h
Whole body	99±10
Brain	96±12
Heart	80±14
Lungs	84±14
Liver	77±10
Spleen	80±11
Kidneys	82±10

Table 2 ^{131}I-chTNT dosimetry of normal organs*

Organ	Absorbed dose	
	$\bar{x}$ ±s /mGy/MBq	Range /Gy
Adrenals	0.48±0.08	0.35~0.97
Brain	0.22±0.04	0.16~0.42
Breasts	0.34±0.06	0.25~0.67
Gallbladder wall	0.48±0.07	0.34~0.96
LLI wall	0.39±0.06	0.27~0.75
Small intestine	0.40±0.06	0.29~0.76
Stomach	0.42±0.07	0.31~0.82
ULI wall	0.41±0.06	0.29~0.81
Heart wall	1.49±0.73	1.06~4.04
Kidneys	1.62±0.56	1.71~4.55
Liver	1.08±0.27	1.18~2.63
Lungs	0.62±0.25	1.55~2.74
Muscle	0.36±0.06	0.26~0.69
Ovaries	0.44±0.04	0.50~0.77
Pancreas	0.49±0.08	0.36~0.94
Red marrow	0.38±0.06	0.44~0.73
Bone surfaces	0.41±0.06	0.29~0.78
Skin	0.29±0.05	0.21~0.57
Spleen	1.87±0.62	0.83~4.16
Testes	0.32±0.05	0.38~0.58
Thymus	0.42±0.07	0.32~0.83
Thyroid	7.58±5.13	0.47~23.09
Urin bladder wall	0.73±0.10	0.62~1.37
Uterus	0.42±0.04	0.50~0.77
Whole body	0.41±0.07	0.30~0.80

*Female 3, male 6, injection dose : (29.6±3.7) MBq/kg

The dosimetry of normal organs and whole body was estimated by Mirdose 3.0 software and the results are listed in Table 2. Within 2d after injection, the mean absorbed dose of red marrow, lungs, skin, thyroid, ovaries and testes are listed in Table 3. Lung tumors can not be visualized clearly at 0.5h, and would be prominent from 2 to 7d (Fig.1). The results shows tumors with the highest uptake of (2.8±2.0)%ID of ^{131}I-chTNT at 24h. The mean absorbed dose of tumors within 2 d, 7 d, 14 d, and 50 a are listed in Table 4. The mean absorbed dose of tumors (within 50 a) was (8.28±2.65) Gy, ranged from 4.22 to 12.81Gy. (65±4)% of it was reached within 7 d, (89±2)% of it was reached within 14 d, and the tumor-to-nontumor ratio (T/NT) was 3.95±1.55 (from 1.63 to 6.29).

Table 3 The absorbed dose of some critical organs within 2d after injection of ^{131}I－chTNT

Patient No.	Injection dose /MBq	Absorbed dose /Gy					
		Red marrow	Lungs	Skin	Thyroid	Ovaries	Testes
1	1110	0.12	0.87	0.09	0.19	－	0.11
2	1772	0.17	0.62	0.13	0.09	－	0.15
3	1406	0.13	0.56	0.10	0.33	－	0.12
4	1621	0.19	0.78	0.14	0.66	0.20	－
5	2405	0.22	0.83	0.17	0.73	－	0.20
6	1454	0.13	0.48	0.10	0.12	－	0.11
7	1228	0.12	0.63	0.09	0.18	－	0.10
8	1247	0.14	0.82	0.10	0.65	0.14	－
9	1258	0.14	0.12	0.11	0.31	0.15	－

Table 4 The mean of absorbed dose of tumors and lungs, and the ratio of tumor-to-nontumor within 2d, 7d, 14d, and 50a after injection of ^{131}I－chTNT

Patient No.	Injection dose /MBq	Mass of tumors /g	Absorbed dose of tumors /Gy				Absorbed dose of lungs /Gy	T/NT
			2d	7d	14d	50a	50a	50a
1	1110	25	0.72	2.84	3.85	4.22	2.59	1.63
2	1772	24	1.51	6.47	9.43	11.07	1.88	5.87
3	1406	26	1.68	6.95	9.69	11.00	1.75	6.29
4	1621	20	1.39	5.87	8.42	9.78	2.74	3.57
5	2405	101	1.81	8.93	11.66	12.81	2.05	6.25
6	1454	16	1.11	4.42	6.05	6.72	1.55	4.33
7	1228	22	0.85	3.43	4.73	5.25	2.12	2.48
8	1247	21	0.85	3.36	4.55	4.99	2.74	1.82
9	1258	28	0.21	5.82	7.90	8.65	2.65	3.27

4 Discussion and conclusion

The fact that the tumor-to-nontumor ratio was 3.95±1.55 confirmed the specificity of ^{131}I-chTNT for lung tumors. The mean absorbed dose of different kinds of tumor was not the same (Table 3), showing that many kinds of histopathologic type tumor can uptake the ^{131}I-chTNT, which confirmed that ^{131}I-chTNT was a universal anti-tumor drug.

Within 2d after injection, the mean absorbed dose of the critical organs (Table2) was smaller than the level of acute radiation damage (red marrow, 1 Gy; lungs, 6 Gy; skin, 3 Gy; thyroid, 5 Gy; ovaries, 3 Gy; testes, 3 Gy), respectively[14]. The maximum of mean absorbed dose of critical organs (red marrow, 0.73 Gy; thyroid, 23.09 Gy; ovaries, 0.77 Gy; testes, 0.58 Gy; kidneys, 4.55 Gy; liver, 2.63 Gy; lungs, 2.74 Gy) were smaller than their fractionated irradiation tolerance dose (40, 30, 6, 2, 20, 35, 20 Gy)[15]. So another administration is possible.

References

1 Hornick J L, Sharifi J, Khawli L A, *et al*. Cancer Biother Radiopharm, 1998, **13**: 255-268.

2 Hornick J L, Sharifi J, Khawli L A, *et al*. J Nucl Med, 2000, **41**: 355-362.

3 Hornick J L, Khawli L A, Hu P S, *et al*. Clin Cancer Res, 1999, **5**: 51-60.

4 Zhu S P, Li Z. (ed). Radiation toxicology. 2nd. Beijing: Atomic Energy Press (in Chinese), 1992: 73.

5 Eary J F, Appelbaum F I, Durack L, *et al*. Med Phys, 1989, **16**: 382-387.

6 Breitz H B, Fisher D R, Weiden P L, *et al*. J Nucl Med, 1993, **34**: 908-917.

7 Wang J X, Chen R S, Zhu H D, *et al*. (ed). Anatomy, physical, and metabolic database of Chinese reference man (in Chinese). Beijing: Atomic Energy Press, 1998: 27.

8 Koral K F, Zasadny K R, Ackermann R J, *et al*. Med Phys, 1998, **25**: 85-91.

9 Nachar O, Rousseau J A, Leflbvre B, *et al*. J Nucl Med, 1999, **40**: 1728-1736.

10 Pan Zhongyun (ed). Clinical nuclear medicine (in Chinese). Beijing: Atomic Energy Press, 1994: 88-96.

11 Stabin M G. J Nucl Med, 1996, **37**: 538-546.

12 Buchegger F, Vieira J M, Blaeuenstein P, *et al*. Eur J Nucl Med, 2003, **30**:239-246.

13 Koral K F, Zasadny K R, Kessler M L, *et al*. J Nucl Med, 1994, **35**: 1714-1720.

14 Xia F N. Radiation protection. in Liu CZ (ed), Experimental nuclear medicine and radiopharmaceutical (in Chinese). Beijing: People's Medical Publishing House, 1999. 48-67.

15 Clifford K S, Carlos C, Luther A P, *et al*. (ed), Wang SL, Liu YP, Sun Q, *et al*. (translated). Radiation oncology—Management decisions. Tianjin: Tianjin Science & Technology Translation and Publishing Corp., 2001: 245-259.