TUMOR NECROSIS THERAPY OF LUNG CANCER USING I-131 LABELED CHIMERIC TNT ANTIBODY

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ABSTRACT

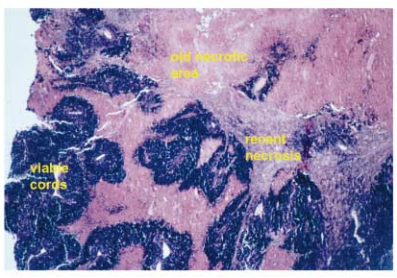
The treatment of advanced lung cancer is still a major challenge in clinical medicine. One promising approach has been the use of Tumor Necrosis Therapy (TNT) to target therapeutic radionuclides to solid tumors. As part of a larger clinical program, 43 patients were treated by 3 different protocols using I-131 chTNT MAb. Diagnosis was confirmed by histology and included 30 cases with stage IIIB and 13 cases with stage IV. Of these patients, 32 cases were newly diagnosed and 11 had prior chemotherapy or radiotherapy. All patients were randomly divided into three groups and treated either with (1) iv infusion (n=22); (2) intratumoral injection using CT guided catheter (n=16); and (3) combination iv (25%) and intratumoral (75%) infusion. All patients received two dosages of radiolabeled MAb using a total dosage of 0.8 mCi/kg on days 1 and 14. All patients had complete radiographic work-up before the initiation of therapy and were assessed at 4 and 10 weeks. PR was defined as a >50% reduction in tumor mass in all lesions and CR as a complete remission for >10 weeks. The results showed that those patients receiving iv injection alone had 2 PR (9%), 16 had stable disease (73%), and 4 progressed (18%). Those receiving intratumoral injection had 1 CR (6%), 8 PR (50%), 7 had stable disease (44%), and 0 progressed. Finally, those in group 3 had 1 CR (20%), 1 PR (20%), 2 (40%) had stable disease, and 1 (20%) progressed. For those patients receiving either intratumoral injection or the combination PR + CR was >50%. Immunoscintigraphy performed on days 4-6 post-injection showed that the tumor/normal tissue ratio in group 1 averaged 1.36 while groups 2 and 3 averaged 14.6 and 9.8, respectively. Toxicity was limited to mild and reversible bone marrow suppression in 20 cases (2 with stage 3 leukopenia and 2 with stage 3 thrombocytopenia). All cases had normal liver, thyroid, and renal tests. Finally, no HACA or HAMA was detected at 1 month and 2 months post-therapy. These promising results demonstrate that sufficient doses of radiolabeled antibody can be safely delivered to tumor to cause significant therapeutic effects in advanced stage lung cancer and that the route of delivery is important to the efficacy of this treatment.

INTRODUCTION

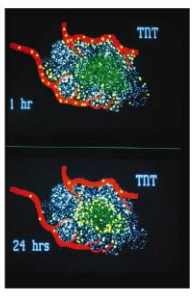
Tumor Necrosis Therapy (TNT) is a novel concept that utilizes monoclonal antibodies directed against intracellular nuclear antigens (DNA/Histones) to target degenerating cells present in tumors. As shown below, solid tumors, unlike normal tissues and organs, consist of three distinct areas: viable cells, recent areas of necrosis, and old necrotic zones. TNT antibodies administered either systemically or intratumorally, enter the tumor mass and bind specifically to cell ghosts present in both new and old areas of necrosis (shown schematically below). Normal tissues which have an active reticuloendothelial system, do not contain degenerating cells for any length of time and are therefore unreactive with TNT antibodies. To demonstrate the specificity of TNT antibodies for necrosis, extensive autoradiographic studies were done in human tumor-bearing nude mice. As shown below, serial sections of tumors removed at various times after I-125 labeled TNT antibody administration show early penetration of radiolabeled antibody in the tumor periphery (6 hours) and later binding of antibody in necrotic zones (2 days). Studies performed after 10 days show marked retention of antibody in necrotic areas while normal tissues (kidney and liver) do not show any uptake. Finally, microautoradiography demonstrates that this uptake occurs in the nuclei of early degenerating cells and that viable cells adjacent to necrotic areas are unlabeled (see below).

In order to determine the therapeutic value of radiolabeled TNT for the treatment of solid tumors in patients, a Phase I/II clinical trial was performed in 43 patients with histologically confirmed lung cancer as described below.

HISTOLOGICAL SECTION OF SOLID TUMOR

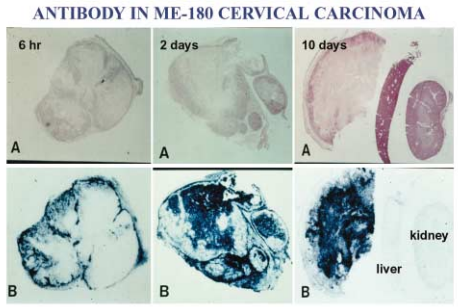


SCHEMATIC DIAGRAM OF TNT UPTAKE IN TUMOR

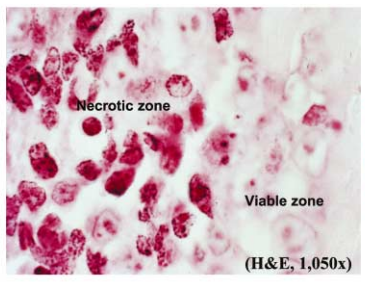


TNT antibody (yellow) enters tumor via leaky vessels and binds to necrotic regions (green).

MACRO-AUTORADIOGRAPHY OF I-125 TNT ANTIBODY IN ME-180 CERVICAL CARCINOMA



MICRO-AUTORADIOGRAPHY OF I-131 TNT-1 IN VIABLE/NECROTIC ZONE INTERFACE

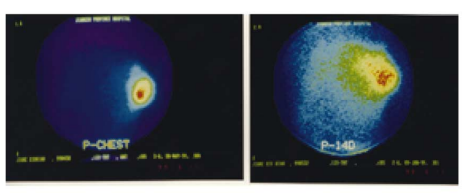


Dark granules over nuclei of non-viable cells demonstrate site of TNT antibody binding.

PATIENTS AND METHODS

Patients Eligibility: A total of 43 patients enrolled into this study had a cytological and histological confirmed diagnosis of stage IIIb (30/43) or IV (13/43) lung cancer. The average patient age was 57.3 years, with a range of 31 to 74 years; 33 (77%) were male. All patients had a Karnofsky index performance status of 60 or better and had an anticipated survival of at least 3 months. As confirmed by fine needle biospy, 24 patients (56%) had a diagnosis of adenocarcinoma, twelve patients (28%) were diagnosed with squamous carcinoma, 6 patients (14%) with small-cell lung cancer, and only 1 patient (2%) with adeno-squamous carcinoma. Patients were allowed to have received radiotherapy more than two months before study entry or chemotherapy more than one month before study entry. All patients had measurable disease on thoracic radiographs or CT scans.

Treatment: All patients had no allergic reactions to iodine. To block uptake of iodine-131 by the thyroid, patients received Lugol s solution orally beginning three days before the therapy and continuing until 7 days after therapy. Each patient also received dexamethasone and diphenhydramine 30 minutes before treatments. Forty-three patients were randomly divided into three groups according to the method of administration. Twenty-two patients in 1st group were administrated by I.V. drug infusion, 16 patients in 2nd group were administrated by intratumor ingestion, and 5 patients in 3rd group received both treatments. The dosage for each patient was 0.8 mCi/kg which was repeated two weeks later. In the 3rd group, 75% dosage was given by intratumor injections and 25% by I.V. infusion. In the I.V. group, the total dose of 131I-chTNT was delivered in 250 ml of normal saline, and the solution was administered through a free-flowing I.V. line. The intratumor injection of 131I-chTNT was directed by thoracic CT using a multiple-hole needle. CT scanning clearly showed tumor localization, the needle pathway, and the site of administration. Using this method, it was possible to use multiple-sites of injection in order to assure adequate spread of radiolabeled antibody throughout the mass of the tumor.



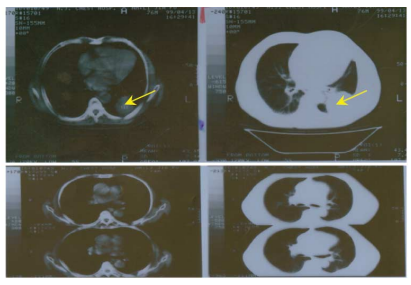
Left Panel: Scintigram of posterior chest showing location of intratumoral injection into lung tumor.

Right Panel Scintigram 14 days later showing remarkable retention of radiolabeled chTNT MAb at site of injection with only moderate radial diffusion.

Treatment Evaluation: Each patient received a thorough physical examination and were evaluated by a panel of laboratory tests, including CBC, routine renal and liver function studies, EKG, bone marrow evalution, CT, and blood HACA/ HAMA. The tumor size was recorded 4 weeks before and 10 weeks after completion of treatment using thoracic radiography and CT. Responses were defined according to the WTO criteria as a complete response (CR), a partial response (PR), no change (NC) and progressive disease (PD).

131I-chTNT systemic biodistribution was determined by thoracic nuclear scans 4-6 days after administration. Regions of Interest were drawn to calculate the ratio of tumor to non-tumor uptake.

Toxicity was graded using WTO toxicity criteria.



Upper Panels: CAT images of lung fields showing site of posterior lung tumor (arrows) prior to radioimmunotherapy.

Lower Panels: CAT images 3 months later after I-131 chTNT radioimmunotherapy showing dramatic shrinkage of tumor mass.

CLINICAL EFFICACY

Table 1: Clinical Results of Three Administration Methods

Administration Method	No. Pts	CR	PR	NC	PD	(CR+PR)%
I.V.	22	0	2	16	4	9.1%
Intratumor injection	16	1	8	7	0	56.3%
I.V.+Intratumor injection	5	1	1		1	40.0%
Total	43	2(4.6%)	11(25.5%)	25(58 1%	5(11.6%	13(30.2%)

The above three groups received two ^{131}I-chTNT treatments at a two week interval. There are statistically significant differences between the iv treated patients and those treated intratumorally alone or in combination.

COMPARISON OF AVERAGE TUMOR/NON-TUMOR RATIOS

Administration Method	Number of Patients	Average T/TN Ratios
Intravenous	19	1.36
Intratumor	15	14.6
Intratumor (75%) and Intra-Venous (25%)	5	9.38

The results show that there is a statistically significant difference in T/NT ratios between I.V. group and intratumor injection group (t=5.1, P<0.01). In these studies, the highest radioactivity was detected in big cardiovascular vessels and liver in the I.V. group. By comparison, there was no obvious radioactivity in the liver and heart areas in the intratumor injection group.

ADVERSE REACTIONS

Administration Method	Number of Patients	WBC 0	WBC I	WBC II	WBC III	PLT 0	PLT I	PLT II	PLT III	Hb 0	Hb I	Hb II	Hb III
Intravenous	22	12	7	1	2	3	15	2	2	9	12	1	0
Intratumoral	16	6	10	0	0	8	8	0	0	5	11	0	0
Intratumoral (75%) and Intravenous (25%)	5	5	0	0	0	4	1	0	0	4	1	0	0
Total	43	23	17	1	2	15	24	2	2	18	24	1	0

Toxicity was graded according to the WTO toxicity criteria. No adverse effects of liver, renal, and thyroid functions were reported among the 43 patients during the 10-week treatment period. None of the 43 patients developed HACA or HAMA responses. Seven patients reported fatigue and appetite loss in the first week of treatment. The major toxicity was hematopoietic in origin as shown above.

CONCLUSIONS

Among 43 patients in this study, 4.56% showed a complete response and 25.5% showed a partial response for an overall efficacy of 30.2%. 58.1% patients has no change and 11.6% patients had progressive disease.

The efficacy in the intratumor injection group was 56.3% compared with an efficacy of 9.1% in the I.V. group. There was a statistically significant difference between the two groups indicating that intratumor injection had a better effect than I.V. administration.

None of the 43 patients developed a HAMA or HACA response. Only transient fatigue, appetite loss, and vomiting were reported which did require treatment.

The major adverse event of 131I-chTNT was bone marrow toxicity. Out of 43 patients treated, only two patients (4.65%) showed grade III neutropenia or thrombocytopenia.

The data presented in this study demonstrate that 131I-chTNT has clinical efficacy in the treatment of lung tumors. Moreover, injection of 131I-chTNT directly into lung lesions showed dramatically high T/NT ratios (14:1), a high efficacy, a low frequency of bone-marrow toxicity, and significantly less adverse experiences compared with systemic chemotherapy.

In conclusion, 131I-chTNT, especially when used intratumorally, appears suitable for the treatment of late-stage lung cancer.