BLEOMYCIN AS A ^{99m}Tc CARRIER IN TUMOR VISUALIZATION

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The oncostatic polypeptide drug, bleomycin, was evaluated as a potential carrier of ^{99m}Tc for scintigraphic visualization of malignant tumors. The drug was labeled with ^{99m}Tc by a tin (II) method. Paper chromatographic analysis showed that most technetium in the preparation migrated similarly as bleomycin.

Following intravenous administration of the ^{99m}Tc-bleomycin, the blood technetium decreased to about 10% dose after 6 hr in cancer patients. In mice bearing a transplanted carcinoma, the tumor/blood concentration ratio of the technetium reached nearly 3 after 6 hr.

Scintigraphy was performed using a rectilinear scanner after 2–4 hr and/or a scintillation camera after 0.5–6 hr following the administration in 18 cancer patients each with one biopsy-proven malignant lesion. Squamous-cell lesions of about 3 cm or less in the throat or the neck constituted 7 of the 18 lesions. Four of the seven were visualized. Ten lesions were in the chest and consisted of a Hodgkin's granuloma, a seminoma, four adenocarcinomas, and four squamous-cell carcinoma lesions. The granuloma, the seminoma, a bronchogenic adenocarcinoma, and two squamous-cell carcinoma lesions were visualized. Generally, whether in the throat and neck or in the chest, visualized lesions were relatively large or superficially located.

The polypeptide antibiotic drug, bleomycin (*1,2*), was recently found to have considerable therapeutic effects against epidermoid carcinomas and malignant lymphomas (*3–7*). The polypeptide nature of bleomycin (*8*) offers a unique possibility for labeling an antineoplastic drug with technetium. Such polypeptides as albumin (*9–11*) and caseidin (*12*) have been labeled with technetium. The present trial study was undertaken to evaluate the bleomycin as a potential carrier of ^{99m}Tc for scintigraphic visualization of malignant tumors.

MATERIALS AND METHODS

For technetium labeling of bleomycin, 1-m*M* Sn(II) solution was prepared by dissolving anhydrous $SnCl_2$ (Matheson Co., Norwood, Ohio) in 0.1-*N* HCl solution. Technetium-99m generator eluate and the 1-m*M* Sn(II) solution were mixed in 3:1 proportion (v/v) for about 5 min. One and one-half milliliters of the "Tc-Sn" mixture was added to 15 mg of lyophilized bleomycin sulfate in an ampule. The bleomycin was obtained from Bristol Laboratories, Syracuse, N.Y. It was a mixture containing bleomycin A_2 as the main component and B_2 as the next major component (*13*). The resultant "Tc-Sn-bleo" mixture (pH about 1.8) was titrated with 0.1-*N* NaOH solution to pH about 2.3 and then stirred under N_2 for about 30 min. The mixture was then applied to an AG1-X8 (Cl^-) column (0.7 × 4.5 cm, Bio-Rad Laboratories) or a Sephadex G25 column (1 × 15 cm) to remove unbound ^{99m}Tc. The AG1-X8 column was washed with 0.008-*N* HCl solution before the application and "eluted" with the same after the application. Similarly, the G25 column was washed and eluted with physiologic saline. Most of the technetium recovered in the eluate appeared in the first 3–4 ml from the AG1-X8 column and in the 4th–7th ml from the G25 column. These fractions were Millipore-sterilized for intravenous use as ^{99m}Tc-bleomycin preparations. Individual patients received less than 15-mg amounts of bleomycin from the administration.

The Tc-Sn mixture, the Tc-Sn-bleo mixture, and the ^{99m}Tc-bleomycin were analyzed on Whatman No.

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l paper in a chromatographic tank purged with N_2. The development was 10 cm in 85% methanol and 20 cm in 10% NH_4Cl solvent. After the development, the paper was cut into pieces and assayed for technetium in a well scintillation counter. According to Umezawa and his associates, bleomycin complex could be separated into A and B groups of components by paper chromatography in 10% NH_4Cl solvent: bleomycin A had R_f values of about 0.88–0.94, and bleomycin B about 0.66–0.70 (*1,2*).

Blood clearance, tissue distribution, and urinary excretion of the ^{99m}Tc-bleomycin were evaluated in Balb/C mice bearing carcinomatous tumors about 50 mm^3 in size or in cancer patients. Techniques used in these studies were similar to those previously described (*11,12*). Imaging in the patient was performed with an Ohio-Nuclear dual 5-in. Model 54D rectilinear scanner or with a Nuclear-Chicago Pho/Gamma camera.

RESULTS AND DISCUSSION

Tin(II) was used for technetium labeling of bleomycin. Lyophilized bleomycin was dissolved in a "blank" mixture of ^{99m}Tc generator eluate and a $SnCl_2$ solution. As shown in Table 1, the labeling took place in the resultant "Tc-Sn-bleo" mixture. In the analysis on papers in 10% NH_4Cl solvent, about 95% of the blank technetium remained at the origin. However, about half of the technetium in the Tc-Sn-bleo mixture migrated away from the origin. The remaining half behaved similarly to the blank technetium and appeared to represent unbound technetium.

When two batches of the blank were applied to an anion-exchange AG1-X8 column and to a Sephadex G25 column, an average of 89% and 96% of the applied technetium was retained by the AG1-X8 and the G25 column, respectively. Accordingly, ^{99m}Tc-bleomycin was obtained by passage of the Tc-Sn-bleo mixture through either column to remove most of the unbound technetium. Of the applied technetium, an average of 48% (range 34–62%, 12 batches) was recovered from the AG1-X8 column, and 35% (range 27–43%, 2 batches) from the G25 column.

Figure 1 shows the results of paper analysis of the ^{99m}Tc-bleomycin preparation. In 10% NH_4Cl solvent, most of the applied technetium migrated in a manner similar to bleomycin A (the dominant peak centered at about $R_f = 0.88$) and to bleomycin B (part of the "hump" over $R_f = 0.60$–0.75). As shown in the analysis in 85% methanol solvent, some pertechnetate regenerated after the column separation.

TABLE 1. PAPER CHROMATOGRAM OF (A) GENERATOR ELUATE ($^{99m}TcO_4^-$), (B) "BLANK" MIXTURE OF GENERATOR ELUATE AND $SnCl_2$ (NO BLEOMYCIN PRESENT), (C) MIXTURE OF GENERATOR ELUATE, $SnCl_2$, AND BLEOMYCIN ("Tc-Sn-Bleo")*

R_f	(A) $^{99m}TcO_4^-$ (2)	(B) Tc-Sn blank (2)	(C) Tc-Sn-bleo (8)
0.00–0.05	0.4	95.9	53.1
0.05–0.10	0.1	0.7	1.3
0.10–0.15	0.1	0.4	0.1
0.15–0.20	0.1	0.3	0.9
0.20–0.25	0.0	0.3	0.8
0.25–0.30	0.0	0.3	0.8
0.30–0.35	0.0	0.3	0.8
0.35–0.40	0.0	0.2	0.8
0.40–0.45	0.1	0.2	0.9
0.45–0.50	0.1	0.2	1.0
0.50–0.55	0.1	0.2	1.1
0.55–0.60	0.2	0.1	1.5
0.60–0.65	0.3	0.1	2.0
0.65–0.70	4.2	0.2	3.2
0.70–0.75	36.4	0.3	4.6
0.75–0.80	53.4	0.1	4.7
0.80–0.85	4.9	0.1	5.7
0.85–0.90	0.0	0.1	6.9
0.90–0.95	0.0	0.1	6.6
0.95–1.00	0.0	0.1	2.4

* Tc-Sn blank and Tc-Sn-bleo (10 mg bleo/ml) had identical pH (2.3) and identical Sn concentration (0.25 mM). Chromatograms were developed in 10% NH_4Cl solvent under high partial pressure of N_2. Number of batches are indicated in parentheses. Mean values of percent applied ^{99m}Tc with indicated R_f values are shown.

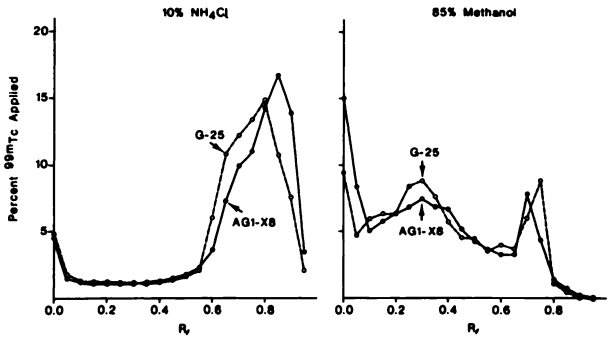

FIG. 1. Paper chromatography of ^{99m}Tc-bleomycin in 10% NH_4Cl or 85% methanol solvent under high partial pressure of N_2. The ^{99m}Tc-bleomycin was prepared by passage of "Tc-Sn-bleo" mixture (described in Table 1) through either anion exchange AG1-X8 column or Sephadex G25 column, which removed most of unbound technetium from mixture. Percent applied ^{99m}Tc with $R_f = x_1 + 0.05$ is shown as mass point at $x_1 = 0.00, 0.05, 0.10$, etc. See text.

The ^{99m}Tc-bleomycin was intravenously administered to mice and patients with malignant tumors. Table 2 shows the tissue distribution of the technetium in the mouse bearing a transplanted KHJJ carcinoma in the flank. A high technetium concentration was reached in the kidneys. The tumor/blood con-

centration ratio of the technetium increased from about 1.7 after 1.5 hr to nearly 3 after 6 hr. Relative to the concentration in the tumor, those in the liver plus spleen, stomach, lungs, and skin were substantial and those in the muscle and brain were small. Three mice excreted an average of 80% dose in 6 hr and 88% dose in 1 day.

Following the administration of ^{99m}Tc-bleomycin in cancer patients (Fig. 2), blood clearance of the technetium was initially rapid with a 50% clearance time of less than 12 min but becoming slower after about 1 hr. Of the administered dose, about 10% (range 8–12%) remained in the blood after 6 hr, about 48% (range 35–54%) of the dose was excreted in the urine in 6 hr, and about 64% (range 53–74%) in 1 day.

Scintigraphy was performed with a rectilinear scanner after 2–4 hr and/or with a scintillation camera after 0.5–6 hr following the administration in 18 cancer patients each with one biopsy-proven malignant lesion. Figure 3 shows whole-body scans in 2 of the 18 patients. The technetium distribution

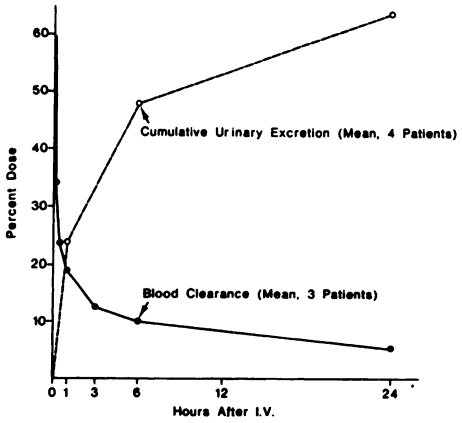

FIG. 2. Blood clearance (% dose remaining in blood) and cumulative urinary excretion of technetium following intravenous administration of ^{99m}Tc-bleomycin in cancer patients.

seen on these scans was grossly similar to that found in the distribution study in mice (Table 2). Patient RB had a small lesion of squamous-cell carcinoma in the left tonsil without evidence of regional lymph node or distant metastases. Lips rather than the tonsillar lesion were seen on the scan (Fig. 3A). ED had a squamous-cell carcinoma lesion in the mediastinum. This large lesion was faintly seen on the scan (Fig. 3C) against normal background in the chest.

Seven of the 18 biopsy-proven lesions were squamous-cell carcinomas of about 3 cm or less in the throat or the neck. Two were small and deep in the throat. The other five were about 3-cm metastases to submandibular or cervical nodes. Four of these five were visualized with the ^{99m}Tc-bleomycin. The remaining three of the seven were not seen on the scintigraph. Figure 4 shows a positive study for a right submandibular lesion in LD. In him, there was a tendency for the ^{99m}Tc-bleomycin to localize in epithelial tissues and squamous-cell carcinomas largely independent of their vascularity.

Ten of the 18 lesions were in the chest. Five of the ten were visualized with the ^{99m}Tc-bleomycin. Of the five visualized lesions, there were two squamous-cell carcinomas, one Hodgkin's granuloma, one metastatic seminoma, and one bronchogenic adenocarcinoma, all in the mediastinum and/or lungs. Although they ranged about 4–7 cm in size, their visualization was rather faint as illustrated by the scan of ED shown in Fig. 3C. The nonvisualized five lesions were a 5-cm metastatic hypernephroma in a right lower lobe close to the liver, a 4-cm metastatic gastric adenocarcinoma adjacent to a scapula, a 3-cm bronchogenic undifferentiated carcinoma in a hilar region, and two squamous-cell carcinomas of less than 2 cm.

The remaining one of the 18 lesions was in an extremity. As shown in Fig. 5, it was visualized as

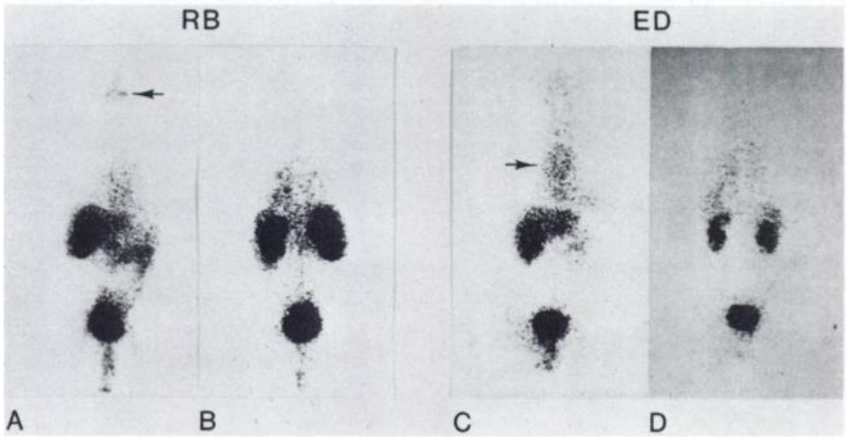

FIG. 3. Anterior (A and C) and posterior (B and D) whole-body scans obtained 3.5 hr after administering 20 mCi of ^{99m}Tc-bleomycin in RB (A and B), and 2.5 hr after 7 mCi in ED (C and D). Arrow in A points to normal lips; arrow in C to 7-cm lesion of squamous-cell carcinoma in mediastinum. See text.

TABLE 2. TISSUE DISTRIBUTION OF TECHNETIUM FOLLOWING ADMINISTRATION OF ^{99m}Tc-BLEOMYCIN IN MICE BEARING TRANSPLANTED TUMOR (KHJJ CARCINOMA)

	% dose/gram*									
Post i.v.	Kidneys	Tumor	Blood	Liv + Spl	Stomach	Lungs	Skin	Femur	Skeletal muscle	Brain
1.5 hr	6.3	3.5	2.0	1.7	1.4	1.3	0.8	0.5	0.3	0.06
6.0 hr	4.8	3.1	1.1	1.9	0.8	0.9	0.5	0.3	0.2	0.04

* Mean of 3 mice.

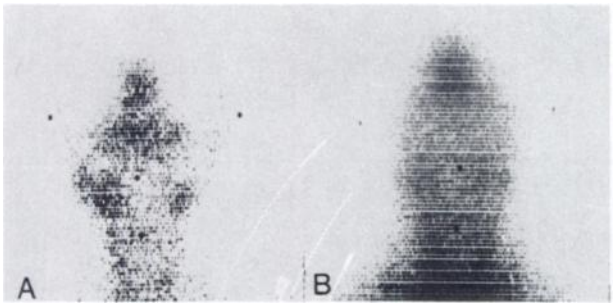

FIG. 4. Anterior rectilinear scans of head (extended) and neck obtained 2 hr after administering 8 mCi of ^{99m}Tc-bleomycin (A) and 0.5 hr after 10 mCi of $^{113m}InCl_3$ (B) in LD with 3 × 4 cm lesion of squamous-cell carcinoma in right submandibular region. Both scans had two midline markers: one over thyroid cartilage notch, another over chin. ^{99m}Tc-bleomycin scan shows preferential uptake in area of right submandibular lesion and that of normal lips and tongue.

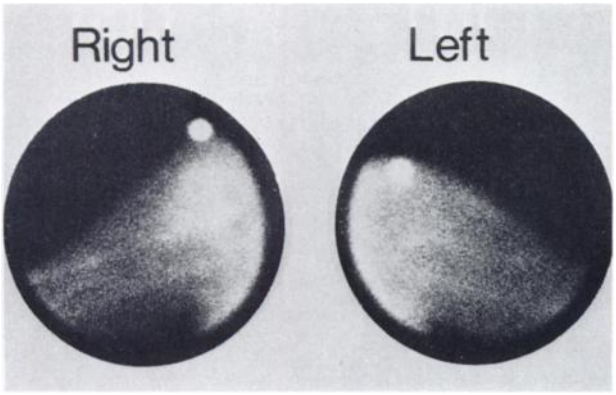

FIG. 5. Anterior scintiphotos of right and left shoulders obtained 0.5 hr after administering 33 mCi of ^{99m}Tc-bleomycin in PD. Markers were placed over acromioclavicular joints. A 3 × 4 cm-lesion of metastatic gastric adenocarcinoma extending into medulary cavity of right humerus was visualized.

early as 0.5 hr following the ^{99m}Tc-bleomycin administration.

The chromatographic analysis shown in Table 1 and Fig. 1 indicates that most of the technetium in the ^{99m}Tc-bleomycin preparation was associated with the bleomycin. In vivo, the technetium exhibited some degrees of preferential localization in the lungs and squamous epithelial tissues (Table 2 and Fig. 3, 4) and a rapid urinary excretion (Fig. 2). Such biological properties had been described for bleomycin (*14–16*).

During the early hours, however, preferential localization of the technetium in malignant tumors of the head and neck and the chest was not remarkable relative to background technetium levels that prevailed in these regions (Fig. 3, 4). Scintigraphic false-negative rate was nearly one-half for the 17 biopsy-proven malignant lesions in these regions. Only relatively superficial or large lesions were visualized (Fig. 3–5). The background was particularly high in the region of the urinary bladder, kidneys, liver, stomach, and heart. The early visualization of the lesion in the right upper arm of PD (Fig. 5) appeared to relate to a relatively low background in the skeletal muscle and bones (Table 2) rather than to the gastric origin of the metastatic lesion.

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