

# THE TREATMENT OF BLADDER CANCER BY NEOTHRAMYCIN

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Neothramycin (NTM), an anthramycin-group anticancer antibiotic, was used in the treatment of superficial carcinoma of the bladder.

NTM was instilled into the bladder in the following dosages. Ten mg NTM in 20 ml of sterile distilled water was given first, and increased to 40 mg in 20 ml. This procedure was performed every second week to twice a day. Recently, in 2 patients, the treatment has been combined with 20 mg NTM intravenous administration.

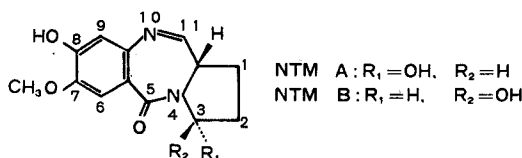
In 4 of the 11 patients (36%) the tumors disappeared completely, while in 6 patients (55%) there was partial disappearance of more than 50% and in one patient (9%) there was no effect. Three of the patients had irritable bladder symptom (temporarily).

NTM was concluded to be effective for superficial carcinoma of the bladder.

**Key words:** Superficial bladder cancer, Intravesical chemotherapy, Neothramycin

Since the treatment of intravesical instillation of thio-TEPA by Jones and Swinney<sup>1)</sup>, the method of topical chemotherapy with several anti-cancer drugs for superficial bladder cancer have been reported and it is now an established method of anti-bladder cancer treatment. This paper presents a summary of the first experience in the treatment of bladder cancer by the intravesical instillation of neothramycin. Neothramycin, abbreviated NTM, is a new anti-cancer antibiotic that was isolated from the culture broth of streptomyces strain MC 916-C4

by Umezawa et al.<sup>2,3)</sup>. It is structurally similar to anthramycin, sibiromycin, tomaymycin etc. of the anthramycin group. The antibiotic contains almost equal amounts of neothramycin A and B. The molecular weight of NTM is 262.1 (Fig. 1). DNA has been reported to be the chemoreceptor of NTM and its reaction rate to be slower than that of other DNA-binding antibiotics, including anthramycin, tomaymycin, sibiromycin, adriamycin and actinomycin<sup>4,5)</sup>. NTM inhibits biosynthesis of nucleic acid, particularly RNA synthesis at the cellular



Neothramycin A: (3S, 11aS)-2, 3, 5, 11a-tetrahydro-3, 8-dihydroxy-7-methoxy-5-oxo-1H-pyrrolo[2, 1-c][1, 4]benzodiazepine  
 Neothramycin B: (3R, 11aS)-2, 3, 5, 11a-tetrahydro-3, 8-dihydroxy-7-methoxy-5-oxo-1H-pyrrolo[2, 1-c][1, 4]benzodiazepine  
 Molecular weight: 262.1

Fig. 1. Chemical structure of Neothramycin (NTM)

level<sup>4,5)</sup>.

### MATERIALS AND METHODS

This study comprised 9 men and 2 women with superficial bladder cancer. The patients were between 55 and 87 years

Table 1. Clinical data of 11 patients

|                          |       |
|--------------------------|-------|
| Age (yrs) :              |       |
| Range                    | 55-87 |
| Av.                      | 72.7  |
| Sex :                    |       |
| M                        | 9     |
| F                        | 2     |
| Grade of differentiation |       |
| Grade I                  | 5     |
| Grade II                 | 6     |

Table 2. Regimen of this study

| Dose of NTM | Interval of instillation                                   | Cases |
|-------------|--|-------|
| 10mg.       | Weekly (1/W)   | 1*    |
| 20mg.       | Daily (1/D)  | 1     |
| 40mg.       | Twice a week, weekly or every other week (2-1/1-2w)        | 3**   |
| 40mg.       | Daily or 6 times a week ( $\frac{1}{D}$ or $\frac{6}{W}$ ) | 6*    |
| 40mg.       | Twice a day (2/D)  | 2     |

\*, ★ : The same cases

old, with a mean of 72.7 years old. Tumor classification was performed with the aid of urethroscopy, ultrasonography, cytologic evaluation of urine and histologic study of transurethrally obtained biopsy specimens. Five patients had grade 1 tumors and 6 patients had grade 2 tumors without evidence of invasion (pTa-pT1b). The tumors were smaller than a walnut (Table 1).

The instillation was first carried out with 10 mg of NTM in 20 ml sterile water once a week. As some favourable effects were observed in the examination of cystoscopy after the first course, the doses of NTM were increased up to 40 mg in 20 ml sterile water. This procedure was performed from twice a day to every other week (Table 2).

The absorption of NTM from the bladder mucosa was studied in 3 patients. The NTM solution which was prepared to make a concentration of 40 mg NTM per 20 ml was instilled for one hour by means of an indwelling catheter.

### RESULTS

Table 3 shows the results. In 4 of the 11 patients (36%), the tumors disappeared completely, while in 6 patients (55%) there was partial disappearance, and in one patient (9%) there was no effect. The response rate was 91 percent.

Table 3. Clinical data and results of treatment

| Cases    | Age | Sex | Grade of differentiation | Size                 | Single or multiple | Dose of NTM (Interval of instillation) [intravenous administration] | Result | Side effect |
|----------|-----|-----|--------------------------|----------------------|--------------------|---|--------|-------------|
| 1. K.Y.  | 71  | M   | G 1                      | Thumb's head         | S                  | 40mg×21 (2/D)   | CR     | Frequency   |
| 2. M.K.  | 77  | M   | G 2                      | Thumb's head         | M                  | 40mg×21 (2/D)   | CR     | Frequency   |
| 3. Y.H.  | 75  | F   | G 1                      | Little-finger's head | S                  | 40mg×12 (6/W)<br>(20mg×7)   | CR     | —           |
| 4. K.N.  | 56  | M   | G 2                      | Thumb's head         | M                  | 40mg×26 (6/W)<br>(20mg×9)   | CR     | —           |
| 5. K.K.  | 61  | M   | G 2                      | Walnut large         | S                  | 40mg×14 (1/D)   | PR     | —           |
| 6. G.N.  | 84  | M   | G 1                      | Walnut large         | S                  | 40mg×6 (1/D)  | PR     | —           |
| 7. M.I.  | 87  | M   | G 2                      | Thumb's head         | S                  | 40mg×24 (6/W)   | PR     | —           |
| 8. M.M.  | 76  | F   | G 2                      | Bean large           | S                  | 20mg×10 (1/D)   | PR     | —           |
| 9. E.E.  | 55  | M   | G 1                      | Rice large           | M                  | 10mg×9 (1/W)<br>40mg×21 (1/2W~2-3/W)                                | PR     | —           |
| 10. U.Y. | 80  | M   | G 2                      | Little-finger's head | M                  | 40mg×10 (1/1-2W)<br>40mg×18 (6/W)                                   | PR     | Frequency   |
| 11. K.O. | 78  | M   | G 1                      | Pea large            | M                  | 40mg×10 (1-2/W)   | NC     | —           |

Table 4. Recurrence after treatment

|               | Result of Treatment |               |                  | NC |
|---------------|---------------------|---------------|------------------|----|
|               | CR                  | P<br>with TUR | R<br>without TUR |    |
| No recurrence | 2                   | 1             | —                | —  |
| Recurrence    | 2                   | 3             | 2                | 1  |

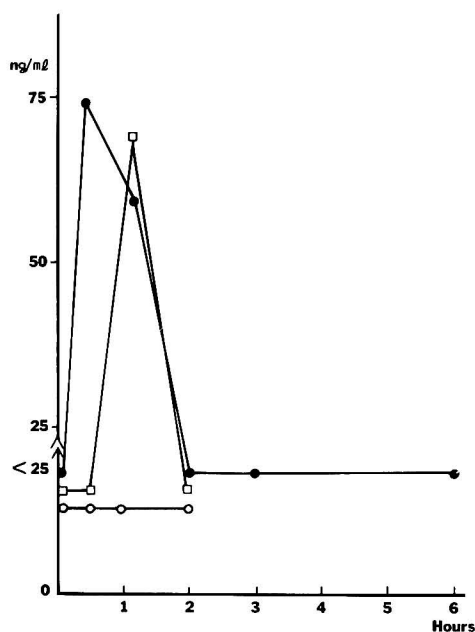


Fig. 2. Serum concentration of NTM after absorption from bladder cavity

Two of the 4 patients who became tumor-free were treated by intravesical NTM 40 mg twice a day, and the others treated by intravesical NTM 40 mg 6 times a week combined with intravenous administration of NTM 20 mg (Table 3).

Three patients experienced irritable bladder symptoms temporarily. In 2 of them, the increasing frequency occurred during treatment which was performed twice a day, and in the other the increasing frequency occurred during treatment which was performed 6 times a week (Table 3).

Two of the 4 patients who became tumor-free were still without recurrence after 6 and 9 months, respectively. In the others, recurrences occurred after 2 and

4.5 months, respectively. In 4 of the 6 patients whose tumors were reduced 50% or more, TUR was performed after this treatment. In one of this group there was no recurrence after 16 months, but in 5 of these patients recurrences appeared after 2.5 to 7 months (mean of 4.4) (Table 4).

Absorption studies were carried out in 3 patients at a concentration of 40 mg NTM per 20 ml. The maximum serum concentration of NTM was 74.9 ng/ml, 69.9 ng/ml in 2 patients, respectively and less than 25 ng/ml in the other patient (Fig. 2).

### CASE REPORTS

Case 1; A 76-year-old woman was admitted to our hospital with gross hematuria. Cystoscopic examination revealed papillary tumor in the right lateral wall. Bladder biopsy revealed transitional cell carcinoma of grade 2. Intravesical instillation of NTM, 20 mg dissolved in 20 ml sterile distilled water was given daily for 10 days.

Fig. 3 shows the cystoscopic findings before and after treatment. The tumor was reduced to approximately half after treatment.

Ultrasonographic view of the lower abdomen showed the tumor, measuring 13 mm in height by 13 mm in diameter before treatment, and measuring 7 mm in height by 8 mm in diameter after treatment (Fig. 4).

Case 2; A 71-year-old man was hospitalized because of gross hematuria and

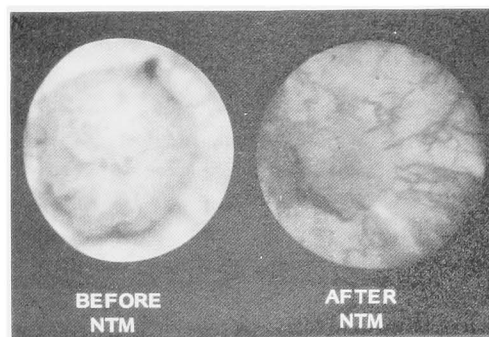


Fig. 3. Cystoscopic findings before and after treatment in Case 1

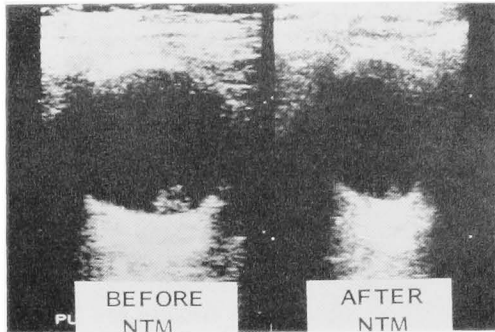


Fig. 4. Ultrasonographic views before and after treatment in Case 1

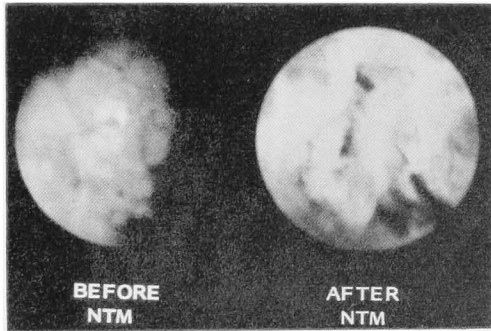


Fig. 5. Cystoscopic findings before and after treatment in Case 2

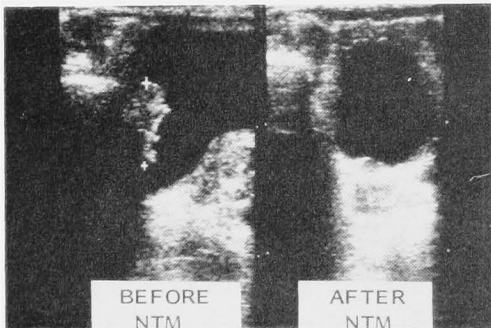


Fig. 6. Ultrasonographic views before and after treatment in Case 2

frequency. Cystoscopy revealed papillary tumor in the right lateral wall. Bladder biopsy revealed transitional cell carcinoma of grade 2. Intravesical instillation of NTM 40 mg in 20 ml sterile water was given twice a day for 21 times.

Fig. 5 shows the cystoscopic findings before and after treatment the tumor has disappeared after treatment.

Ultrasonographic view demonstrated a large tumor, measuring 21 mm in height by 31 mm in diameter before treatment. The tumor has disappeared after treatment (Fig. 6).

#### DISCUSSION

Intravesical Thio-TEPA was first used to treat bladder cancer in 1961. Although intravesical Thio-TEPA was found to be effective, serious effects, chiefly myelosuppression, hindered its clinical application.

The molecular weight of Thio-TEPA may be related inversely to the absorption rate. Yeates reported that molecular size determined absorption from the bladder and the substances absorbed from the bladder have molecular weights of under 200<sup>1)</sup>. The molecular weight of Thio-TEPA is 189 and it should, therefore, be absorbed<sup>6)</sup>. The molecular weight of NTM is 262.1 and, therefore, it should not be absorbed. However, there is a little absorption of NTM from the bladder mucosa. Absorption studies were carried out in 3 patients at a concentration of 40 mg NTM per 20 ml of sterile water. The NTM solution was then instilled for one hour by means of an indwelling catheter. More than 74.9 ng/ml NTM was not found in the blood of 3 patients.

When NTM was administered intravenously, gastro-intestinal disturbance such as nausea and vomiting were the most frequent adverse reactions<sup>7)</sup>. There was no severe toxicity to the liver, kidney, heart or central nervous system. There was, therefore, no systemic side effects due to absorption of NTM<sup>7)</sup>.

When NTM was administered intravenously in rabbits, the highest levels were shown in the kidney and urinary bladder, which might have been due to urinary excretion<sup>8)</sup>. We had experienced that the size of supraclavicular lymphonodi metastasis of bladder tumor was decreased by administration of NTM intravenously.

Therefore, the effect of combined NTM given intravesically and intravenously was expected to be excellent compared with instillation alone. Complete regression

was observed with the combination therapy in 2 patients.

Three of the 11 patients had irritable bladder symptoms during treatment. All recovered, however, and bladder capacity gradually normalized one or two months after the instillation ceased. The absence of systemic and severe local side effects is an advantage in treatment with NTM.

In the present study there was recurrence of bladder tumor in 2 of 4 patients who became tumor-free and in 3 of the 4 patients who had partial regression after treatment as an adjuvant to transurethral resection. Our limited experience does not permit definite conclusions concerning the tumor-prophylactic effect of intravesical NTM, but NTM seems to have little value as a prophylactic agent to prevent recurrences of bladder cancer. It is clear from our series of patients that NTM is at least as safe and effective as any other drugs which have been tried.

We reported a summary of this paper at the 6th Congress of European Association of Urology 1984.

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## Neothramycin による膀胱癌の治療

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表在性膀胱癌に対し anthramycin 系に属する抗癌性抗生物質 Neothramycin (NTM) を使用した。

NTM の膀胱内注入療法で用いた投与量は以下のごとくである。初回には NTM 10 mg を滅菌蒸留水 20 ml に溶解させて膀胱内に注入し、副作用がないため 40 mg に増量した。投与間隔は 2 週に 1 回からはじめ、1 日 2 回の膀胱内注入を行なった。最近の 2 例

に膀胱内注入療法に加えて NTM 20 mg の経静脈性全身投与の併用療法を試みた。

成績は 11 例中著効 4 例 (36%)、50% 以上の縮小が認められた有効 6 例 (55%) で、無効 1 例 (9%) であった。副作用としては 3 症例に一過性の膀胱刺激症状が認められた。

表在性膀胱癌の治療には NTM が有効な薬剤であると考えられる。

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