Acta Urol. Jap. Vol. 26
No. 5, May, 1980

EFFECT OF PEPLEOMYCIN (BLEOMYCIN DERIVATIVE, NK 631) ON PROSTATIC CANCER

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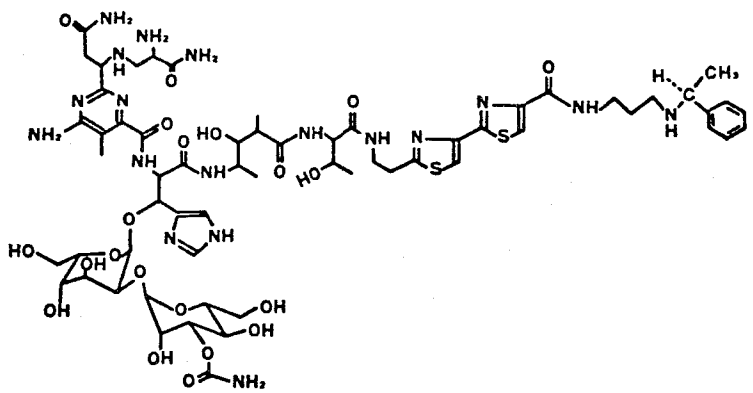
Since the new bleomycin derivative-pepleomycin was reported to be effective for experimentally induced adenocarcinoma of stomach in rats, it was administered in two cases of prostatic cancer. Satisfactory response was obtained in well differentiated carcinoma, meanwhile only histological effect was observed in undifferentiated one. It seems that the effect of pepleomycin on prostatic cancer was brought about by the suppression of DNA synthesis of tumor and also of pituitary function resulting in decreased androgen secretion from Leydig cells.

Pepleomycin[4] is one of the derivatives of bleomycin as shown in Fig. 1, which is claimed to have less pulmonary side effect. Ichikawa[3] speculated and demonstrated that bleomycin is highly accumulated in squamous cell and therefore is specifically effective for squamous cell carcinoma in clinical cases. However, newly developed pepleomycin has been proved effective for experimental gastric cancer in rats, histological pattern of which is adenocarcinoma. Because of this effectiveness for adenocarcinoma, authors have used this agent for two cases of prostatic adenocarcinoma. It is the purpose of this paper to report clinical courses of these two cases and effectiveness of this anticancer drug for prostatic carcinoma.

CASE REPORTS

Case No. 1 (M. S.), 75-year-old Japanese man first visited our clinic on June 15, 1978 with complaints of dysuria, pain on urination, pollakisuria and pain in left thigh of two months duration.

On physical examination, his general condition was excellent. Blood pressure was 140/70. No abnormal masses were



NK-631

3- [(s)-1 -Phenylethylamino]-propylamino-Bleomycin

Fig. 1. The chemical structure of pepleomycin.

Table 1. Laboratory data of two cases.

	Case No. 1			Case No. 2		
	before the treatment (1978-6-15)	during the treatment (1978-7-15)	after the treatment (1978-8-14)	before the treatment (1978-9-22)	during the treatment (1978-10-19)	after the treatment (1978-11-28)
I. Urinalysis						
protein	−	−	±	−	+	±
glucose	−	−	−	−	−	−
RBC	20~25	10~15	many	2-4	8-12	6-8
WBC	2~3	many	30-40	20-30	many	many
epithelia	1~2	1-3	1-3	2-3	0-1	0-1
bacteria	+	+++	−	−	+	++
II. CBC						
RBC ($\times 10^4$)/mm^3	422	460	473	400	394	287
hematocrit %	38	41	39	40	40	28
WBC/mm^3	6800	8200	7100	6200	8500	8400
platelets ($\times 10^4$)/mm^3	24.2	23.6	33.4	24.5	25.8	23.7
reticulocytes ‰	10	16	39	28	12	32
III. Hemorrhagic diasthesis						
bleeding time		1'00"	1'30"	3'30"	4'30"	1'00"
active partial thromboplastin time		32.1"	37.9"	36.9"	44.1"	37.3"
prothrombin time		10.4"	9.4"	11.5"	11.1"	11.6"
IV. Blood chemistry						
total protein g/100ml	6.6	7.2	7.0	7.1	7.0	6.7
A/G	1.4	1.3	1.0	0.9	0.8	0.9
BUN g/100ml	17.3	17.9	22.7	16.1	23.2	16.2
creatinine mg/100ml	0.7	0.6	0.6	0.7	0.9	1.1
Na mEq/L	141	140	140	142	138	137
K mEq/L	3.9	5.0	4.7	4.5	3.2	3.6
Cl mEq/L	105	98	102	103	104	101
GOT/GPT	13/5	16/6	18/3	32/26	25/13	39/15
alkaline phosphatase K.A.U.	14.0	10.3	8.2	4.7	4.9	5.0
acid phosphatase K.A.U.	26.8	13.1	9.6	7.9	12.2	13.0
LDH I.U.	322	415	313	301	296	324

V. Arteriol blood gas analysis							
pH		7.398	7.429	7.428	7.441	7.421	7.480
PCO_2	mmHg	38.6	37.1	37.7	34.1	33.1	30.5
PO_2	mmHg	90.3	99.1	111.3	85.7	94.4	85.1
HCO_3^-	mmol/L	23.4	24.2	24.6	22.9	21.2	22.5
base excess	mmol/L	-0.9	0.3	0.6	-0.4	-2.2	-0.6
oxygen saturation	%	95.5	97.1	97.6	95.9	96.5	96.2
VI. others							
ESR	mm/hr.	15	32	77	30	35	50
CRP		-	+	++	+++	++	+++

palpable in the abdomen. There was a movable smooth hard lymph node swelling of walnut size in the left inguinal region. Both testes were atrophic. Right epididymis was slightly indurated at its tail. The prostate was markedly enlarged and fixed with bony pelvis with irregular surface. A hard mass of the prostate was well palpable bimanually.

His past history revealed the operation for sinusitis at the age of 18 years, following which he suffered from renal disease. He had gonorrhea at the age of 25 years, and has been suffering from hemorrhoids for the past 20 years.

As his family history, his father died of cardiac disease at 86 years old. His mother died of hypertension at 58 years old. He has 4 brothers and 4 sisters. Two brothers have had hypertension. One sister has been suffering from asthma.

Laboratory data on admission and during the hospitalization are summarized in Table 1. The abnormal data at the time of admission were urinary sediment con-

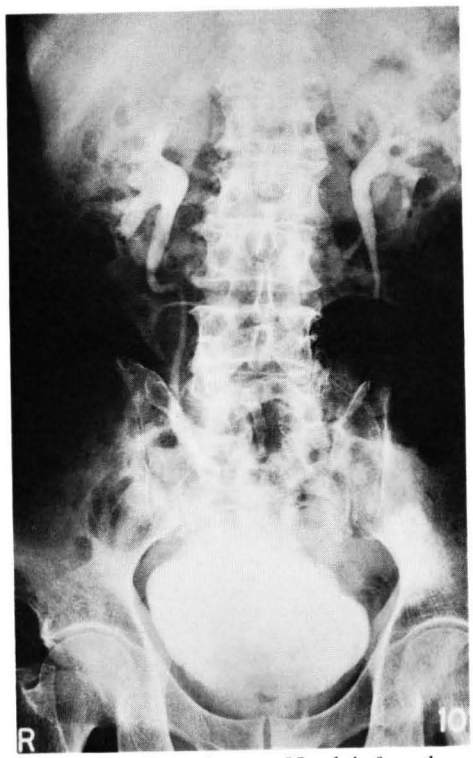


Fig. 2. DIP of the case No. 1 before the treatment.

taining RBC (20~25 per hiyh power field), WBC (2~3) and Cocci, ESR 15/1hr, CRP (+), serum alkaline phosphatase 14.0 K.A. U. (norm.: 2.7~10.0), and serum acid phosphatase 26.8 K.A.U. (norm: 1.0~4.0), No abnormalities were noted in EKG and chest x-ray. KUB and DIP (Fig.2) showed normal upper urinary tract. Cystogram showed irregular protrusion of the prostate. There were metastases to the second lumbar vert ebra, pelvic bone and both femurs. Retrograde urethrogram (Fig. 3a) revealed irregular elongation and nar rowing of the prostatic urethra with marked protrusion of the prostate into thebladder.

Bone scan on June 27 demonstrated abnormal radioisotope accumulation in the right third and the left fourth ribs, thoracic and lumbar vertebrae, pelvic bone and bilateral femurs. Liver scan on July 3 was nega-

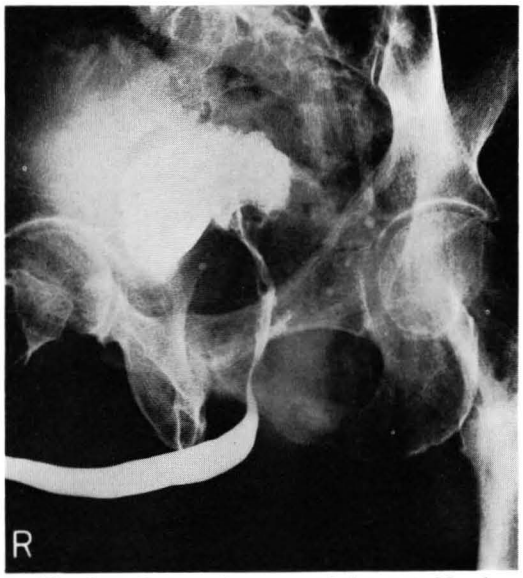


Fig. 3a. Cystourethrogram of the case No. 1 before the treatment.

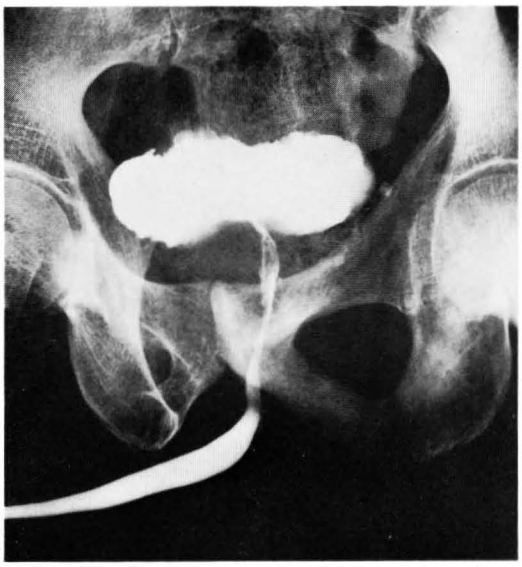


Fig. 3b. Cystourethrogram of the case No. 1 after the treatment.

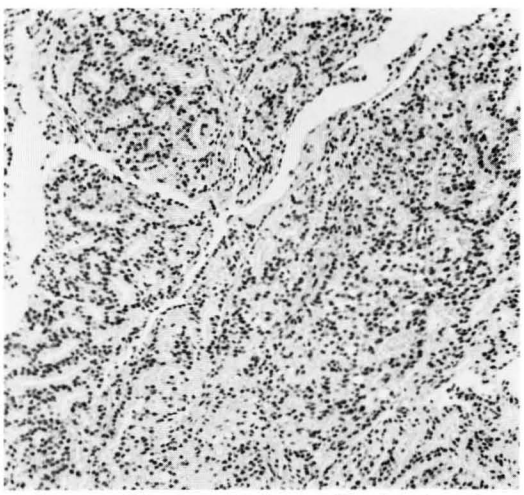


Fig. 4a. Histology of th case No. 1 before the treatment. 90×

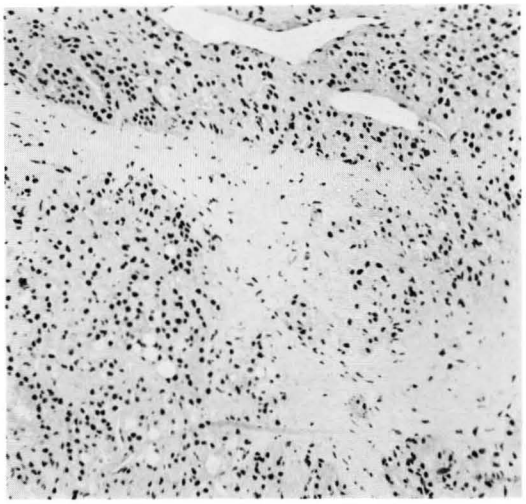


Fig. 4b. Histology of the case No. 1 after the treatment. Note pyknosis, vaculization of the cancer cells and the increased interstitial tissue. ×90

tive.

Transrectal prostatic needle biopsy performed on June 26, 1978 was diagnosed as well differentiated adenocarcinoma (Fig. 4a). From the above findings, stage D prostatic cancer was confirmed. He was started on pepleomycin regimen on June 28, 1978. pepleomycin was given intravenously 10 mg three times a week until August 11, 1978. The total dosis of pepleomycin amounted ot 200 mg. Pro-static cancer was shrunken and left inguinal node became softer a week after the initiation of pepleomycin. With 2 weeks treatment, serum acid phosphatase was reduced to approximately half the initial value and decrease of serum alkaline phosphatase was also noted. His appetite began to decline at the third week. At the 5th week of treatment, itchy papules appeared in palms and back, which gradually became hard scaly skin lesions as shown in Fig. 5. At the same time slight stomatitis occurred. These changes im proved after cessation of the treatment. No other serious side effects were noted in physical and laboratory examinations.

One week after the completion of the treatment, the prostate was smaller than half the original size on admission. Infiltration to the surrounding structure became less and the prostate was mobile on bimanual examination. Left inguinal node was also much smaller and softer. Urethrogram after the treatment (Fig. 3b) revealed improvemrnt of the prostatic tumor. Clinically dysuria improved markedly. Main laboratory data during the course of the treatment are shown in Table 1.

Prostatic biopsy on August 14, 1978 showed degenerative change of cancer cells with nuclear pyknosis, vacuolization of cytoplasm, less eosinophilic cytoplasm, indiscrete intercellular boundaries and increased interstitial tissue (Fig. 4b).

Case No. 2 (S. W.), 74-year-old Japanese man was first seen at our outpatient depart-

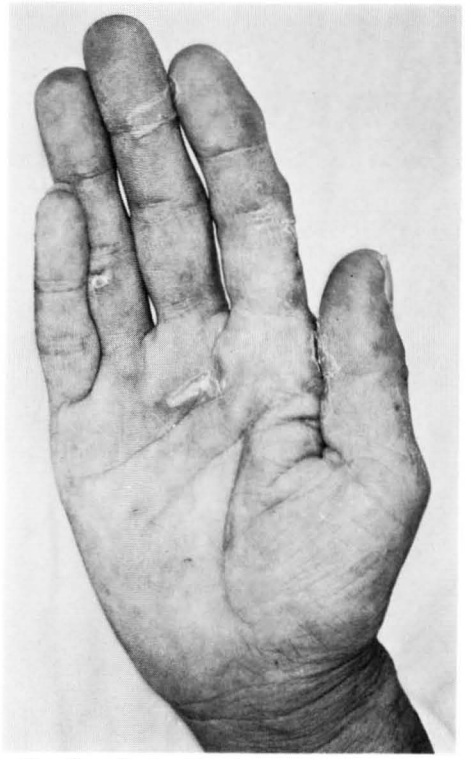


Fig. 5a. Scaly skin changes in the palm.

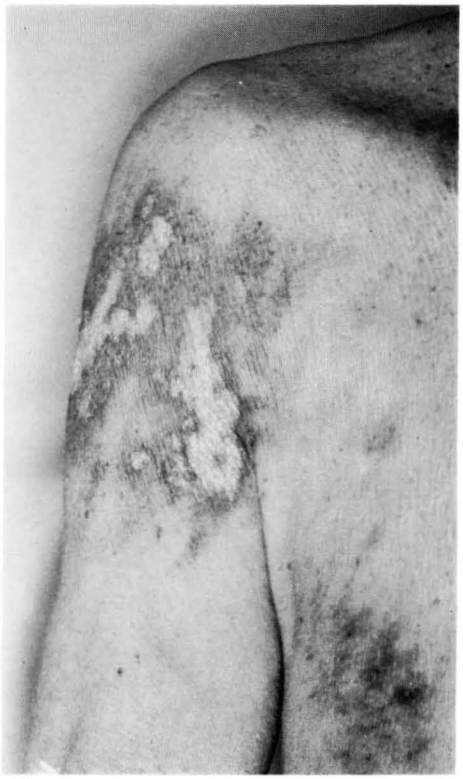


Fig. 5b. Scaly skin changes surrounded by pigmentation in the left shoulder.

ment on August 19, 1978 with the complaint of dysuria, pain on urination and sense of incomplete voiding of 2 months duration. Since his prostate was enlarged and hard, he was admitted to our hospital on September 21, 1978.

His past history revealed subtotal gastrectomy for cancer in July, 1974 and pneumonia in January, 1978. His family history was noncontributory.

On physical examination, his general condition appeared well. Blood pressure was 150/70 with regular pulse rate 78/min.. No anemia, jaundice or edema was observed. There were no abnormal lymph node swellings. Lungs were clear to percussion and auscultation. Neither cardiomegaly nor heart murmurs was noted. There was an upper midline scar in the

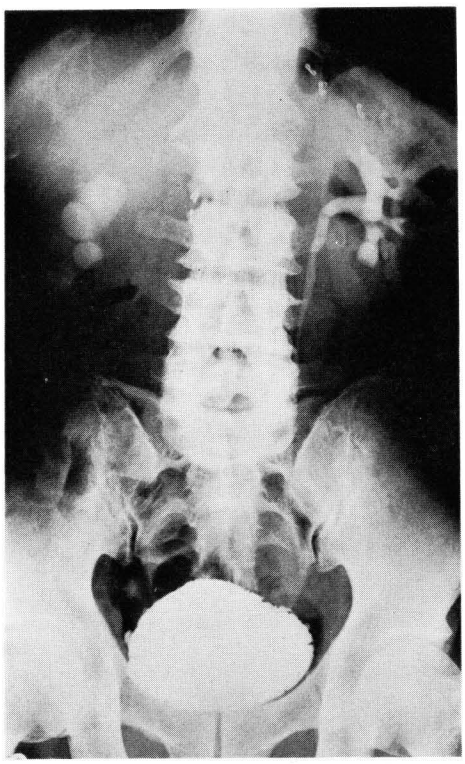


Fig. 6. DIP of the case No. 2 before the treatment. Mild hydronephrosis was noted in the right kidney.

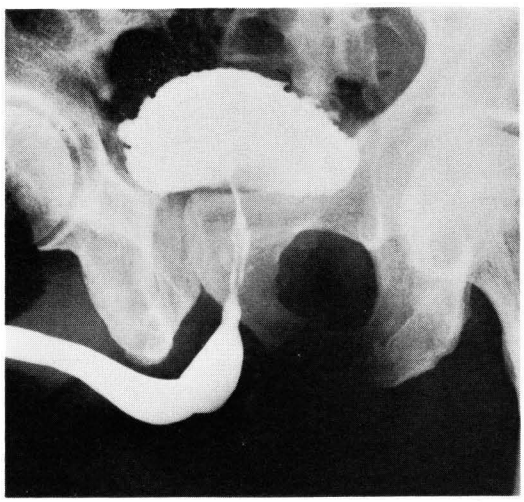


Fig. 7. Cystourethrogram of the case No. 2 before the treatment.

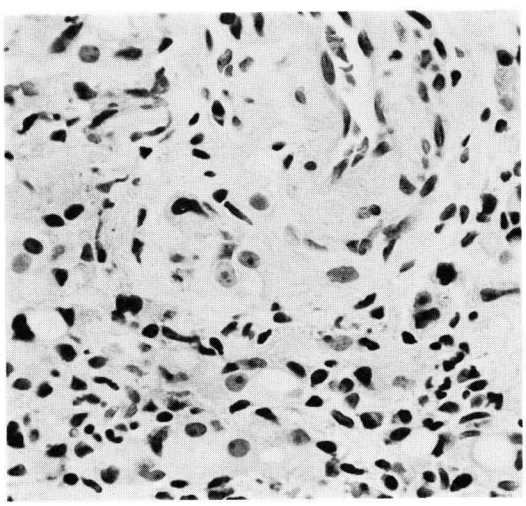


Fig. 8a. Histology of the case No. 2 before the treament. 375×

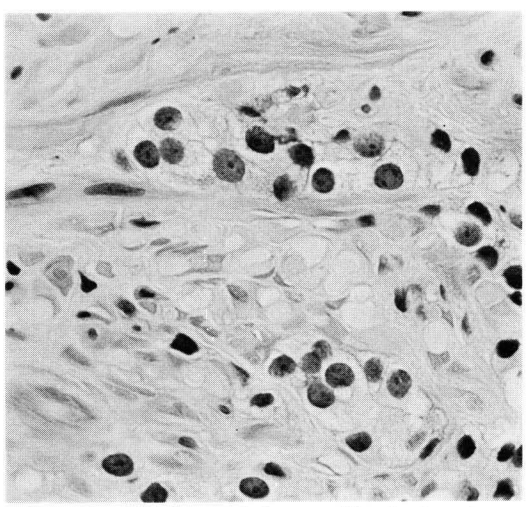


Fig. 8b. Histology of the case No. 2 after the tretment. 375×

abdomen. No abnormal masses were palpable in the abdomen. The prostate was moderately enlarged and was hard with irregular surface. It was bimanually palpable and was fixed with the bony pelvis.

His laboratory data were summarized in Table 1. Main abnormal data before the treatment were urinalysis revealing protein (±), RBC (2~3), WBC (many), bacteria (++), WBC in blood 12300/mm^3, ESR 30/hr, CRP (+++), BUN 23.7mg/100 ml and residual urine 80 ml. Serum acid phosphatase was 5.3 K.A.U.. Chest x-ray and EKG were negative. DIP on September 25, 1978 (Fig. 6) revealed mild right hydronephrosis and prostatic protrusion in cystogram. Retrograde urethrography revealed elongated straight prostatic urethra with irregular intravesical bulging (Ftg. 7). Bone scintigraphy on September 26, 1978 showed multiple faint and small hot-areas of thoracic vertebrae and a faint hot-area in right sacroiliac joint. Liver scan was free from abnormal radioisotope accumulation.

Transrectal prostatic needle biopsy done on September 22 was reported as poorly differentiated adenocarcinoma (Fig. 8a). As the patient had stage D prostatic carcinoma, he was placed on pepleomycin treatment. It was started on September 29, 1978 with a dosis of 10 mg given intravenously three times a week. As of November 17, 1978, total dosis of 200 mg of pepleomycin was had been administered.

The prostatic tumor did not respond to the treatment so well as in the Case No. 1. However, it was softer and slightly smaller one week after the initiation of the therapy. At the end of the third week, the residual urine was 30 ml and there was improvement of dysuria. As side effects, he had fever of 100°F on the first injection but not later on. At the middle of the fourth week, he had slight stomatitis. He showed no skin rash. At the fifth week, his residual urine further decreased to 10 ml. The prostatic tumor was obviously softer and smaller at end of the treatment, although serum acid phosphatase level at this time was higher than that at the time of the treatment initiation. DIP and urethrogram on November 17, 1978 proved less prostatic protrusion into bladder though right hydronephrosis remained unchanged. In post-treatment prostatic biopsy specimens, more than half of the tumor cells showed degenerative change with nuclear and cytoplasmic vacuolization (Fig. 8b).

DISCUSSION

It has been confirmed that the antiandrogenic treatment[1,2] advocated by Huggins in 1942 is quite effective for most of prostatic cancer. However, VACURG[5] reported untoward effect of estrogen on cardiovascular system which may shorten survival of patients. Secondly, there are always some patients of prostatic cancer who do not respond to the antiandrogenic therapy from the beginning. Also, other cases of prostatic carcinoma initially respond to the antiandrogenic therapy but in due time become resistant to the treatment. Because of these two reasons, there has been a strong need for the development of a new agent against prostatic cancer. In that sense, the advent of the new bleomycin-pepleomycin should not be underestimated, since it was shown that this agent was effective to a certain degree in these two prostatic cancer cases. It is difficult to judge whether or not it is more effective for prostatic cancer than estrogen in our study.

The mechanism of pepleomycin to act on prostatic cancer has been considered to be a direct action on tumor cells through the suppression of DNA systhesis. On the other hand, the main action of estrogen on prostatic cancer is postulated by the mediation of pituitary suppression rather than the direct effect on tumor cells. Therefore, there is a possibility that pepleomycin might be effective to prostatic carcinoma resistant to the antiandrogenic therapy.

However, in our two cases, LH, FSH and testosterone were reduced during the pepleomycin administration as shown in Table 2. It is possible that pepleomycin might partly act on prostatic cancer

Table 2. The change of serum LH, FSH and testosterone levels of two cases.

		Case No. 1		Case No. 2		
		before the treatment (1978-6-21)	after the treatment (1978-8-11)	before the treatment (1978-9-22)	during the treatment (1978-10-23)	after the treatment (1978-11-22)
LH	mIu/L	12.7	4.5	22.4	12.9	16.0
FSH	mIu/L	22.2	5.0	22.0	13.0	13.1
testosterone	ng/100ml	600	345	874	545	400

through pituitary suppression. In spite of this fact, pepleomycin has definitely a suppressive actionon DNA synthesis of tumor cells, as it was proved to be effective to adenocarcinoma of the stomach in rats and other tumors which were not reactive to hormonal treatment[4]. We presume that the action of pepleomycin on prostatic cancer is transmitted through the suppression of both DNA synthesis and pituitary function.

As for the side effect, pepleomycin is claimed to cause much less pulmonary complications. In our two cases, pulmonary function was carefully checked periodically by spirometry and gas analysis of arterial blood. Chest x-ray was also taken every week. By these studies, no abnormalities were found during the course of the therapy. No side effects were also noted in hepatic and renal functions, though mild anemia was observed in the Case No. 2 at the end of the treatment. Accelerated erythrocyte sedimentation rate and positive CRP observed in the Case No. 1 are considered due to skin lesions and stomatitis caused by this agent. No cardiovascular changes were also observed. However, long term effect should be carefully followed up in the future.

It seems that this agent is also more effective for well differentiated adenocarcinoma, since the Case No. 1 responded to it better than the Case No. 2 who had undifferentiated adenocarcinoma. This question should be also left to the future investigation.

Pepleomycin was kindly supplied by Nihon Chemical and Pharmaceutical Company, Japan.

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(Accepted for publication, January 25, 1980)

和文抄録

前立腺癌に対する Pepleomycin (Bleomycin Derivative, NK-631) の効果

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未治療の前立腺腺癌2症例に本剤を投与し，その効果を検討した．

症例1：71歳，排尿困難，左大腿部痛を主訴として1978年6月15日当科受診．前立腺は超鶏卵大，石様硬，表面不整，骨盤へ浸潤．左ソケイ部にくるみ大の硬いリンパ腺を触知．骨シンチで多数の転移を認めた．前立腺の針生検組織像は分化型腺癌であった．pepleomycin 200 mg（1回 10 mg，静注，週3回）の投与により前立腺癌，左ソケイ部リンパ腺の著明な縮小がみられ，血清酸ホスファターゼ値が治療前 26.5 K.A.U. から 9.5 K.A.U. まで低下した．治療終了後の生検組織像は癌細胞の変性，壊死組織の線維化が目立った．

症例2：74歳，排尿困難で1978年8月19日当科受診．前立腺は鶏卵大，硬，周囲に浸潤．骨シンチで転移巣が多数あり，前立腺生検組織像は未分化型腺癌であった．pepleomycin 投与で自覚症状は症例1ほどの改善はみられず，前立腺癌そのものもあまり縮小しなかったが，残尿は 80 ml から 10 ml へ減少した．治療後の前立腺生検所見でも癌細胞の空胞化が著明に認められた．

なお副作用としては症例1では著明な皮膚変化がみられたが，症例2でぎ軽度の口内炎を認めるにとどまった．

NK 631 投与前後で血中 FSH, LH, testosterone を測定したところ，両症例ともに投与終了後 FSH, LH, testosterone 値は投与前値の約 1/2 となっていた (Table 2)．つまり，NK 631 の抗腫瘍作用は DNA 合成抑制によるということになっているが，前立腺癌に対する抗腫瘍効果は NK 631 の下垂体抑制による睾丸の Leydig cell よりの androgen 分泌抑制も関与している可能性があることが示唆された．本剤の下垂体抑制効果については今後検討されるべき課題であると考える．