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Clinical Efficiency of Combined Therapy of Bleomycin and Oxygen in Uterine Cancer

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The direct intra-arterial injection of antitumor drugs for treatment of cancer was first reported by Klopp in 1950[1], and then Cromer et al. (1952)[2] reported that more beneficial effects for pelvic tumors were received by administrating of antitumor drug via a intra-arterial route than the intravenous route. Sullivan et al. (1952)[3] reported on the injection of antitumor drugs into the regional arteries for treatment of far advanced cancer, and subsequently many authors reported similar methods, describing usefulness of this therapy for far advanced pelvic cancer.[4][5][6] Thus, the intra-arterial therapy elicited encouraging results for malignant tumors, especially recurrent and progressive malignant tumors of the pelvic.[7][8]

On the other hand, Creech (1958)[9] used an extracorporeal circulation unit (heart-lung apparatus) to isolate the tumor circulation from the body circulation. And he perfused antitumor drugs in high concentration into regional tumor tissue for a short time by applying this method. He reported that the effect of antitumor drugs could be enhanced by the high oxygen tension in tumor tissue. Recent interest lies in the hyperbaric therapy regarding high oxygen concentration in tumor tissue. The chief advantage of oxygen at high pressure (hereafter, OHP) in treatment of malignant tumors is that it increases the susceptibility of tumor cells to radiation. It was demonstrated also by many workers that the sensitivity of tumor cells to X-ray under OHP circumstance were about three times as high as under anoxic conditions,[10][11] and that the antitumor effect of chemotherapy was enhanced with OHP.

Bleomycin (hereafter, BLM), an antitumor antibiotics derived from *streptomyces verticulus*, was discovered by Umezawa in 1965.[12] This drug has been used clinically in the treatment of squamous cell carcinoma and malignant lymphoma.[13] As for knowledge of BLM's mechanism of action, it is reported that BLM inhibits DNA synthesis and produces DNA strand scission,[14] and that this action is stimulated by oxygen and free radical producing systems including superoxyde radicals, and is prevented by radical scavegers.[15]

Taking the above into account, this study was performed to investigate the clinical effects of the combination therapy of OHP and the continuous intra-arterial infusion of BLM.

MATERIAL

Fifty-one patients in Stage II–III of uterine cancer admitted to the Ryukyu University Hospital from October, 1974 to October, 1977 were studied. Patients' age ranged from 31 to 65 years and the average age of the patients was 46 years. There were 32 cases in stage II and 19 cases in stage III.

Twenty cases were treated with the continuous intra-arterial infusion of BLM alone. Thirteen of 20 cases underwent the radical hysterectomy and pelvic lymphadenectomy after the BLM infusion therapy. The rest 7 of 20 cases underwent radiation therapy after BLM infusion (Table 1). Twenty-eight cases were treated by the combined therapy of the continuous intra-arterial infusion of BLM and OHP. Seventeen of 28 cases underwent the radical hysterectomy and pelvic lymphadenectomy after the combined therapy. The rest 11 of 28 cases underwent radiation therapy after the combined therapy. Besides, three cases were treated by the combined therapy of the continuous intra-arterial infusion of MMC and OHP. Two of 3 cases underwent radical hysterectomy and pelvic lymphadenectomy after the combined therapy. One of 3 cases underwent radiation therapy after the combined therapy (Table 2). The radical hysterectomy was performed about 2 weeks after the treatment of both BLM alone and the combined therapies.

METHODS

After the skin had been anesthetized with procaine, a venula 18 gauge needle was introduced directly into the femoral artery. A catheter is then threaded through the needle and passed through the femoral artery to a point approximately 2 to 3cm above the bifurcation of the abdominal aorta, and then the needle was removed. The catheter was made of polyethylene tubing with an inside diameter of 0.25mm and an outside diameter of 0.5mm. One 5mg shot of dissolved BLM was infused. The catheter was connected with the pump, and total 300mg BLM with urokinase 12,000 IU was administered for 7 days through the catheter.

For OHP treatment, we used a Nihon Sanso INC. type KS-305 pressure chamber. This chamber has a capacity of 8 atmospheres absolute (hereafter, ATA) and is large enough to perform an operation. The pressure schedule called for 10 minutes of compression, 50 minutes of full pressure maintenence, and 15 minutes of decompression. Each patient remained for a total 75 minutes in the chamber which was pressurized at 2 ATA. The chamber was pressurized with air instead of pure oxygen for a safety precaution to prevent explosion. The patients respired 100% oxygen at 15 liters per minute by mask all the while in the chamber. The patients were observed through the chamber window.

RESULTS

Among the therapy groups, there was no difference of clinical course, the incidence of objective tumor regression, decrease of vaginal discharge and genital bleeding and pain relief, nor was difference of clinical effects among the histological types. However, patients were divided to two groups, good responders and non responders by the clinical and histological response to the chemotherapy.

In the stage III group treated with BLM alone therapy, responders mean survival time was 38

months and that of non responders was 3.3 months. In the stage III group treated with the combined therapy of BLM and OHP, responders mean survival time was 34.8 months and that of non responders was 7 months. In the stage III group treated with the combined therapy of MMC and OHP, responders mean survival time was 21 months.

In the group treated with BLM alone, 13 of 20 patients went through the operation (Table 1). Three patients of them had positive pelvic lymphnode involvement and 1 of these 3 patients has survived for 50 months without reccurrence of the disease. Four patients of 13 patients died and 2 of the 4 patients had not the lymphnode metastasis. One patient of these 2 patients received the radical hysterectomy on 23 days after the infusion of BLM. The size of her cervix tumor proved to be reduced to one half of the size compared with the size before the BLM infusion. But she had metastasis to her lung at 4 months postoperation. She refused to take any more treatment and died at 5 months after the operation. The another of the 2 patients went through the radical hysterectomy on 7 days after the infusion of BLM and died of cachexia at 3 months after the operation.

And 3 of 7 patients who were treated with irradiation for inoperable condition have survived without reccurrence.

The group of the patients who recieved the combined therapy of the continuous intra-arterial infusion of BLM and OHP is showed at Table 2. Seventeen patients were operable and 11 patients were inoperable. Four of 17 patients who were operated had positive pelvic lymphnode

Table 1. Intraarterial BLM infusion therapy

Patient	Age	Stage	Type of carcinoma cells	Drug and total dose (mg)		Subsequent therapy	Lymphnode involvement	Survival (mo.)	
O.R.	31	II	spinal	BLM	300	radical operation + irradiation	–	63	alive
S.H.	48	〃	transitional	〃	〃	〃	–	61	〃
U.E.	36	〃	〃	〃	〃	〃	–	57	〃
T.A.	42	〃	〃	〃	〃	〃	–	53	〃
K.A.	31	〃	〃	〃	〃	〃	–	52	〃
N.A.	48	〃	〃	〃	〃	〃	–	52	〃
T.A.	52	〃	〃	〃	〃	〃	+	50	〃
S.H.	51	〃	〃	〃	〃	〃	–	56	〃
N.A.	46	〃	spinal	〃	〃	〃	–	51	〃
S.U.	40	〃	transitional	〃	〃	〃	–	18	dead
S.A.	42	〃	〃	〃	〃	〃	+	10	〃
A.R.	52	〃	〃	〃	〃	〃	+	37	〃
T.A.	58	〃	〃	〃	〃	〃	–	3	〃
T.A.	56	III	〃	〃	〃	irradiation		50	dead
I.N.	47	〃	〃	〃	〃	〃		49	alive
H.I.	54	〃	spindle	〃	〃	〃		6	〃
M.A.	50	〃	〃	〃	〃	〃		4	dead
O.S.	37	〃	transitional	〃	〃	〃		3	〃
H.I.	50	〃	spindle	〃	〃	〃		3	〃
C.H.	40	IV	transitional	〃	〃	〃		6	〃

Table 2. Intraarterial BLM or MMC infusion with OHP therapy

Patient	Age	Stage	Type of carcinoma cells	Drug and total dose (mg)		OHP (No.)	Subsequent therapy	Lymphnode involvement	Survival (mo.)	
S.H.	38	II	spinal	BLM	300	15	radical operation + irradiation	–	60	alive
H.I.	51	〃	〃	〃	〃	〃	〃	–	36	〃
M.A.	59	〃	〃	〃	〃	10	〃	–	59	〃
S.H.	39	〃	〃	〃	〃	〃	〃		59	〃
C.H.	54	〃	transitional	〃	〃	〃	〃	+	60	〃
O.S.	42	〃	〃	〃	〃	〃	〃	–	49	〃
O.K.	58	〃	〃	〃	〃	〃	〃	–	54	〃
A.K.	46	〃	〃	〃	〃	〃	〃	+	52	〃
K.A.	41	〃	〃	〃	〃	〃	〃	–	46	〃
A.K.	40	〃	spindle	〃	〃	15	〃	–	63	〃
G.O.	40	〃	〃	〃	〃	5	〃	–	61	〃
K.U.	40	〃	〃	〃	〃	15	〃	–	60	〃
O.S.	41	〃	〃	〃	〃	5	〃	–	60	〃
M.A.	59	〃	transitional	〃	〃	10	〃	+	12	dead
T.A.	37	〃	〃	〃	〃	〃	〃	–	1	〃
T.E.	50	〃	〃	〃	〃	〃	〃	+	19	〃
S.H.	41	〃	spindle	〃	〃	15	〃	–	4	〃
N.A.	53	III	transitional	〃	〃	10	irradiation		42	alive
K.U.	45	〃	spindle	〃	〃	〃	〃		59	〃
Y.O.	41	〃	spinal	〃	〃	15	〃		7	〃
O.Y.	45	〃	transitional	〃	〃	〃	〃		16	〃
N.I.	31	III	〃	〃	350	10	〃		3	〃
H.I.	55	〃	spindle	〃	300	〃	〃		3	〃
M.I.	45	〃	transitional	〃	〃	〃	〃		3	〃
S.A.	47	〃	〃	〃	〃	〃	〃		6	〃
Y.A.	40	〃	〃	〃	〃	〃	〃		10	〃
Y.O.	51	〃	〃	〃	〃	〃	〃		12	〃
Y.A.	59	〃	spindle	〃	〃	〃	〃		0	〃
T.A.	65	II	transitional	MMC	40	15	radical operation + irradiation	–	63	alive
T.O.	46	〃	spinal	〃	20	〃	〃	–	59	dead
M.I.	52	III	transitional	〃	〃	〃	irradiation		20	〃

involvement and 2 of the 4 patients have survived, one with and another without recurrence of the disease.

Three patients of 17 cases died without the lymphnode involvement, one patient died of the allergic shock of peniccilin on 40 days after the radical hysterectomy and another died of acute yellow atrophy of liver at 3 months after the operation and the rest patient died of short bowell intestinal perforation caused by irradiation in 2.5 years after the irradiation therapy.

Two of 3 patients who were treated with the combined therapy of MMC and OHP were operated and recieved post-operative irradiation. One of the 2 patients died from intestinal perforation caused

by the irradiaion and another has survived without reccurrence. The other one patient was inoperable. She was treated with the combined therapy of MMC infusion and OHP, and then irradiated 5,000 rads of ^{60}Co. But there was no response, therefore she was treated additionally with the intra-arterial infusion of 300mg BLM. Unfortunately she suffered from lung fibrosis and died at one month after the BLM infusion.

Table 3 shows side effects in each group. Alopecia, fever, hyperpigmentation, thickening of skin, anorexia and nausea were seen slightly more in the groups of the combined therapy of BLM and OHP than in the group of the BLM alone therapy. Leukopenia was seen only in the group of the combined therapy of MMC and OHP. Every patient was made the periodical examination of Hb, RBC, WBC, GOT, GPT, TP, BUN and PO_2. There was no extreme abnormality in these examinations.

DISCUSSION

When we use the intra-venous infusion method, we need very large doses of antitumor drugs for expecting good effects, and also side effects increase. The administration of antitumor drugs into the regional artery makes it possible to perfuse the high concentrating of antitumor drugs into the carcinoma tissue.

The carcinoma of the uterine cervix is supplied with blood through the branch of abdominal aorta, and primary cervical cancer is localized ordinarily at the area of distribution of this branch. Therefore, instillation of anti-tumor drugs into the regional artery can produce greater effects in uterine cancer than intra-venation of a simillar dose.

In gynecology, the direct intra-arterial infusion of drugs for the treatment of cancer was first reported by Cromer et al.[2], in 1958 Krakoff[8] inserted a catheter to the bifurcation of the abdominal aorta and injected nitrogen mustard. Then, in 1960 Sullivan[3] inserted a catheter through the femoral artery to the hypogastric artery and injected methotrexate with citrovan intermittently. They reported usefulness of this therapy for far advanced pelvic cancer.

Meanwhile, there are two kinds of anti-tumor drugs, that is, one is dependent on time and another is dependent on concentration.[16] The antitumor action of BLM which has been isolated from a strain of *streptomyces verticillus* has tendency to depend on both time and concentration.[17] These results were investigated in vitro. Takabe (1976)[18] reported that BLM showed better response in

Table 3. Toxic effects from BLM with or without OHP therapy

	BLM without OHP		BLM with OPH		MMC with OHP	
	Number	(%)	Number	(%)	Number	(%)
Alopecia	18/20	(90.0)	46/48	(95.8)	0/3	(0)
Fever	15/20	(75.0)	38/48	(79.2)	0/3	(0)
Dermal Complication	12/20	(60.0)	37/48	(77.1)	0/3	(0)
Anorexia or Nausea	14/20	(70.0)	36/48	(75.0)	0/3	(0)
Leukopenia	0/20	(0)	0/48	(0)	1/3	(33.3)

long term infusion rather than in short term infusion of the same dose. According to Drevinko (1972),[19] the long term infusion of BLM works better response, because the continuous pelvic arterial infusion of BLM can give lethal damage to the carcinoma cells which go through G_2-M phase. Huntington (1973)[20] gave BLM to 21 cases with inoperable squamous cell carcinoma by means of the intra-arterial infusion. The infusion was continued over 5 days. And he reported that partial regression was seen in one vulva cancer and one vagina cancer, but no regression was seen in cervix cancer irradiated previously. It was thought that uneffectiveness of the intra-arterial BLM infusion in these cases was owing to blood vessels destroied by previous irradiation.[21] Many authors[22][23] reported that this continuous intra-arterial infusion method was useful for the therapy of far advanced gynecological carcinoma.

Some kinds of anti-tumor drugs and X-ray irradiation have biochemical similarity in their effects. Since the formation of oxidizing free radicals is potentiated by high oxygen tension in tissue,[24][25] the therapeutic effects of some kinds of antitumor drugs and X-ray irradiation are significantly increased dependent upon the concentration of dissolved oxygen in tumor tissue. But the oxygen tension in tumor tissue is commonly less than in normal tissue, therefore, therapeutic effects of irradiation and antitumor drugs could be thought to become more effective when supplied well with oxygen.

Thereafter, many authors[26][27][28][29] reported that increasing the oxygen tension in tumor tissue enhanced the effects of antitumor drugs and irradiation, and that since OHP treatment increased oxygen tension in tumor tissue[30] it was more effective when OHP method was combined with antitumor drugs.[31] The mechanism which OHP enhances the effects of antitumor drugs with is not well known, although it is said that OHP produced free radicals[25] and the effect of BLM is enhanced in the existence of oxygen and free radicals.[32][33]

In the group treated with BLM alone, 3 patients had positive pelvic lymphnode involvement and 2 of them died of the reccurrence of carcinoma. In the group treated with BLM and OHP combination, there were 4 patients who had positive pelvic lymphnode involvement. Two patients of them alive. One patient died of perforation of bowel after the ^{60}Co irradiation, but she was confirmed to be free of carcinoma. Seeing the above, we think that BLM and OHP combination therapy might work better than BLM alone treatment in the survival time.

A number of cases in which regression of tumor were observed, was not significantly different in each treatment group. Five of 11 patients in stage III treated with the BLM and OHP combination therapy showed especially good response to the irradiation, and the degree of tumor regression was seemed to be larger in this group than in other groups.

Side effects such as hyperpigmentation, thickening of skin, fever and depilation caused by BLM and MMC themselves were seen slightly and these side effects disappeared within 3 months post-infusion. In combination treatment group, side effects on skin and hair were seen slightly more than BLM alone treatment group.

The combined chemotherapy of a few drugs is said to work more benefically than a single agent chemotherapy. Therefore, we have recently tried to add one single shot of MMC to the continuous intra-arterial infusion of BLM and OHP combination therapy.

Though the number of patients in this study are too small for us to include definitely, we do suggest that our combination therapy might be appropriate for far advanced carcinoma of the uterine cervix.

SUMMARY

Fifty-one patients of uterine cervix cancer were treated with the combined therapy of OHP and BLM, in addition to the radical operation or irradiation. BLM was administered by the continuous intra-arterial infusion.

The clinical efficiency of this therapy was studied and discussed. Thought the number of patients on this study are too small for us to conclude definitely, we do suggest that our combination therapy might be appropriate for carcinoma of the uterine cervix, especially for far advanced carcinoma.

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