ORIGINAL

Can Kampo therapy prolong the life of cancer patients?

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Abstract : Our policy regarding the performance of radiotherapy to squamous cell carcinoma of the uterine cervix has not changed since 1969. We have already reported the treatment results which were as good as those from other institutions. Since 1978, Kampo therapy was first introduced in the treatment of cancer patients in dealing with problems such as the side effects of radiotherapy and chemotherapy and various types of general malaise. We analyzed our treatment results in order to re-evaluate the chemo-radiotherapy in combination with Kampo. Survival rates for 5, 10 and 15 years, respectively, were 90.9%, 71.6% and 71.6% for Stage IB, 78.9%, 61.8% and 41.8% for Stage II, 62.3%, 49.1% and 41.2% for Stage III and 53.1%, 36.5% and 16.7% for Stage IV.

The Kampo significantly extended the survival of patients with uterine cervical cancer. We intend to perform further research with more patients to explore how this therapy contributes to the prolonging of patients survival. J. Med. Invest. 55 : 99-105, February, 2008

Keywords **:** *cervical cancer, radiotherapy, kampo, sho, long-term outcome*

INTRODUCTION

Radiotherapy has played an important role in treating carcinoma of the uterine cervix and has contributed to an improvement in the cure rate (1-3). Radiotherapy, however, also has its limitations in the treatment of progressive cancer, as does surgery. Accordingly, extensive studies on radiation sensitizers and adjuvant therapy have been performed, including radiation therapy combined with chemotherapy or immunotherapy.

Kampo (Chinese herbel medicine) therapy was first introduced in the treatment of cancer patients from 1978. At the beginning, Kampo applications for cancer therapy were developed by trial and error because of dissatisfaction with Western medicine in dealing with problems such as the side effects of radiation therapy and chemotherapy and various types of general malaise. However, routine treatment produced results which were better than expected (4, 5). This led to rising expectations for the " mysteries" of Kampo. As increasing numbers of reports are now becoming available on cancer radiation therapy, ranging from basic research to clinical studies (6-9), our colleagues and we decided to do a retrospective study of the life-prolonging effects of concomitant treatment with Kampo medicine in combination with Western medicine. The current report shows the results of not a randomized trial that was carried out to evaluate whether Kampo could prolong survival in patients with uterine cervical cancer.

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MATERIALS AND METHODS

From 1978 to 1998, 174 patients with cervical cancer were treated at the Tokushima University Hospital. All patients with squamous cell carcinoma of the cervix were treated with radiotherapy in combination with Kampo and analyzed for this study. Patients with the Federation Internationale de Gynecologie et d'Obstetrique (FIGO) Stage, there were 11 patients with Stage IB disease, 11 patients with Stage IIA, 51 patients with Stage IIB, 9 patients with Stage IIIA, 60 patients with Stage IIIB, 17 patients with Stage IVA, and 15 patients with Stage IVB. Patient age ranged from 34 to 92 years of age (mean, 67 years of age).

For historical controls, we selected 231 patients treated during the same period in our department who did not receive Kampo. There were 12 patients with Stage IB disease, 26 patients with Stage IIA, 64 patients with Stage IIB, 9 patients with Stage IIIA, 61 patients with Stage IIIB, 40 patients with Stage IVA, and 19 patients with Stage IVB. Patient age ranged from 35 to 87 years of age (mean, 67 years of age) (Table 1).

Table 1. Patients characteristics and treatment methods

	Kampo therapy (+)	Kampo therapy (–)
Number of patients	174	231
Age range (median, years old)	34-92 (67.2)	35-87 (66.7)
30≦	1	5
40≦	11	13
50≦	28	37
60≦	48	64
70≦	67	88
80≦	18	24
90≦	1	-
Clinical stage (FIGO)		
Ib	11	12
IIa	11	26
IIb	51	64
IIIa	9	9
IIIb	60	61
IVa	17	40
IVb	15	19
Concurrent chemotherapy	40	32
Maintenance chemotherapy	60	71
Maintenance immunotherapy	125	100

Radiotherapy

The radiotherapy for these patients was essentially based on the combination of intracavitary brachytherapy (ICBT) and external pelvis irradiation.

ICBT was started 1-3 weeks after external pelvis irradiation. T.A.O. manual afterloading applicators (10) with low-dose cesium 137 sources were used routinely for the ICBT. ICBT was performed on a fractionation schedule with one insertion per week, giving 3 to 4 fractions during a period of external pelvis irradiation. The patients received 45-50 Gy at point A through ICBT, with the external pelvis irradiation being designed to bring the dose to a total of 40-50 Gy through use of a center shield. The ICBT dose contribution to the pelvic lymphnodes was also calculated and additional external pelvis irradiation to the node was given to bring the total dose to 60-70 Gy.

External pelvis irradiation was delivered with 6-MV X ray 16×16 to 16×18 cm antero-posterior and postero-anterior ports in a daily fraction of 1.8-2.0 Gy, 5 fractions/week for 4 to 5.5 weeks. External irradiation consisted of whole-pelvis irradiation and pelvis irradiation with central shielding. A center shield of 3 cm width was arranged to avoid from the beginning in stage I-II patients and at 30 Gy in stage III patients. For external irradiation, the weight of whole-pelvis irradiation was increased and that of ICBT decreased as the stage became advanced and tumor volume increased. Since 1981 when computed tomography (X-CT) scans were introduced at our hospital, para-aortic lymph node metastasis has been diagnosed and treated with external irradiation, with doses 50 Gy delivered over 5 to 6 weeks.

The radiotherapy treatment method used at the Tokushima University Hospital has remained essentially unchanged for the past 30 years except for a decrease in the ICBT dose from 58.5 Gy to 43.8 Gy on average after 1969 in order to reduce complications (11, 12).

Adjuvant therapy

From 1979 to 1991, 34 patients with locally advanced cancer (stages IIB, III and IV) underwent systemic chemotherapy concurrently with radiotherapy. This system B-M therapy consisted of bleomycin and mitomycin-C (bleomycin 5 mg intramuscularly daily for 7 days and the next eighth day mitomycin-C 10 mg intravenously) was employed 1 to 4 cycles (13, 14).

From 1987 to 1997, 21 patients with locally advanced cancer received intra-arterial chemotherapy (I-A chemotherapy) concurrently with radiotherapy. The I-A chemotherapy consisted of a combination of 50 mg/body cisplatin and 8 mg/body

mitomycin-C administered simultaneously into the bilateral internal iliac arteries using the balloon occluded arterial infusion (BOAI) method. The infusion was performed twice during radiotherapy in 3-week intervals (15).

In regards to chemotherapy, maintenance therapy was started in 1978, at which time we reduced the dose delivered by ICBT. A total of 161 patients underwent oral administration of 300 mg/day fluorouracil or 300 mg/day tegafur uracil as a maintenance chemotherapy, which was performed continuously for two years following radiotherapy provided no side effects were observed.

Since 1978, we have been using immunotherapy, Krestin (PSK) (16), LC-9018 (17) and Z-100 (18) as Biological Response Modifiers (BRM) combination therapy for radiotherapy. From 1978 to 1990, 178 patients were treated by oral administration of 3-6 g/day PSK and performed continuously for one year as a rule.

Kampo therapy

Kampo applications for cancer treatment were developed by trial and error because of dissatisfaction with Western medicine in dealing with problems such as the side effects of radiation therapy and various types of general malaise.

The Kampo formulation used were Tsumura Kampo granulated extracts, given at a dose of 7.5 to 9.0 g/day, 30 minutes before meals, in a small quantity of hot water. Almost all patients began this regimen during radiation therapy and continued to follow it for several years, up to over 20 years in some cases. Typical Kampo formulations were constitution builders such as Juzentaihoto, Ninjinyoeito and Hochuekkito with usage designated as traditional diagnosis "SHO" for both Wazai and Shazai type formulations (19) (Table 2).

Table 2. Typical Kampo formuration

Kampo formurations	No. of patients
Juzentaihoto	74 (42.5%)
Hatimijiogan	30 (17.2%)
Ninjinyoeito	22 (12.6%)
Saireito	20 (11.5%)
Hochuekkito	11 (6.3%)
Shosaikoto	9 (5.3%)
Daisaikoto	3 (1.7%)
others	20 (11.5%)

Follow-up

All patients had follow-up for more than 5 years (minimum 2 to 312 months). Most patient status was followed once a month for 3 years, then once every 2 to 3 months for 3 years, 2 to 3 times a year for 5 years, and once or twice a year for more than 5 years after radiation therapy. The examination consisted of cystoscopy of the bladder, proctoscopy or barium enema of the colon and rectum, and routine blood, urine, and radiographic examinations. Patient status information was obtained from our records, by letter, or by telephone contact with patients or their relatives.

Analyses

Survival times were calculation by setting the starting point at the initiation of radiation therapy while survival probability was calculated using the Kaplan-Meyer method (20). The statistical significances of difference in survival rates were calculated using the Breslow-Gehan-Wilcoxon tests (21, 22).

In the present study, we compared the outcomes of the Kampotherapty(+) group with those of the Kampotherapy(–) group. As this study was not a randomized trial, any possible deviations were corrected with multivariate analysis using Cox' proportional hazard model (23), and the degree of contribution of each factor to the prognosis was calculated. The following patient characteristics were considered for inclusion in the model : age, clinical stage, concurrent chemotherapy (systemic chemotherapy + I-A chemotherapy), maintenance chemotherapy and maintenance immunotherapy. Factors exhibiting a difference at the 0.05 level were considered statistically significant.

RESULTS

Initial analysis

Fig. 1. show cumulative survivals of patients treated with Kampo V.S. without Kampo ($p < 0.0001$).

Survival rates for 5, 10 and 15 years after treatment with Kampo, respectively, were 90.9%, 71.6% and 71.6% for Stage IB, 78.9%, 61.8% and 41.8% for Stage II, 62,3%, 49.1% and 41.2% for Stage III and 53.1%, 36.5% and 16.7% for Stage IV.

For comparison, survival rates for 5, 10 and 15 years after treatment without Kampo, respectively, were 83.3%, 75.0 % and 64.3% for Stage IB, 66.7%, 42.8% and 23.3% for Stage II, 41.0%, 28.2% and

12.9% for Stage III and 20.3%, 11.9% and 2.0% for Stage IV. Analysis of cumulative survivals of patients with and without Kampo therapy is shown in Figs. 2, 3 and 4.

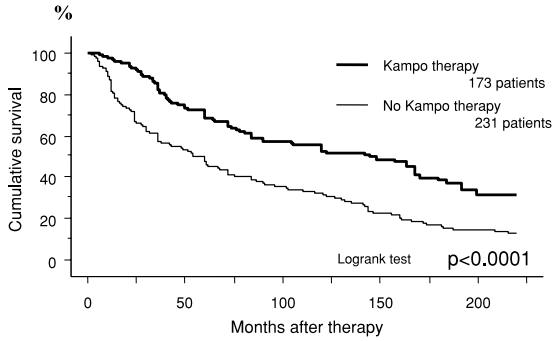

Fig. 1. Overall survival in cervical cancer

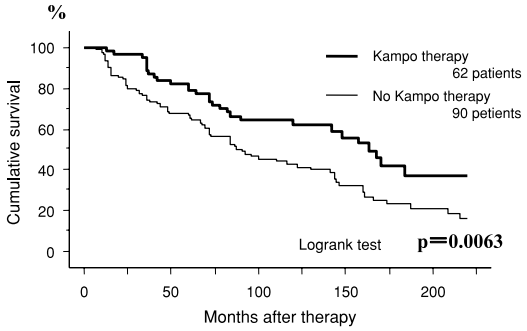

Fig. 2. Overall survival in cervical cancer (Stage II)

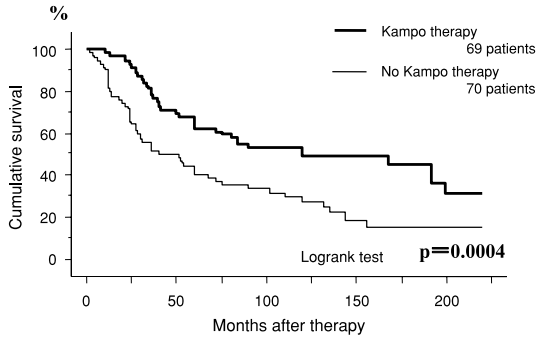

Fig. 3. Overall survival in cervical cancer (Stage III)

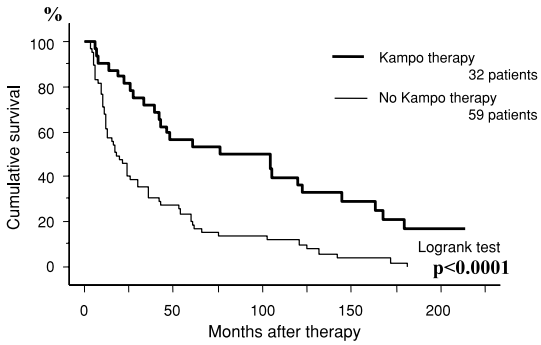

Fig. 4. Overall survival in cervical cancer (Stage IV)

Patients Characteristics

Table 1 shows characteristics of the 405 patients according to the two treatment group comparisons. Of the 174 to receive Kampo therapy, 40 were to receive concurrent chemotherapy, 60 were to receive maintenance chemotherapy and 125 were to receive maintenance immunotherapy, as 32 of the 231 to receive no Kampo therapy were to receive concurrent chemotherapy, 71 were to receive maintenance chemotherapy and 100 were to receive maintenance immunotherapy.

Patients out-comes

Patients out-comes are shown in Table 3. For patients received Kampo, number of patients alive without the evidence of local recurrence and distant metastasis, death of local recurrence and distant metastasis, death of other cause and unknown were 56(32.2%), 58(33.3%), 39(22.4%) and 21(12.1%), respectively.

For comparison, patients received no Kampo, number of patients alive without evidence of local recurrence and distant metastasis, death of local recurrence and distant metastasis, death of other cause and unknown were 25(10.8%), 120 (51.9%), 67(29.0%) and 19(8.2%), respectively.

Table 3. Patients out-comes

Number of patients	Kampo therapy(+) 174	Kampo therapy(–) 231
Range of follow up period (median month)	6-264 (104)	2-312 (75)
Out-comes		
Alive	56 (32.2%)	25 (10.8%)
Cancer death	58 (33.3%)	120 (51.9%)
Other death	39 (22.4%)	67 (29.0%)
Unknown	21 (12.1%)	19 (8.2%)

Univariate analyses

Table 4 shows the univariate analyses of survival using the Breslow-Gehan-Wilcoxon tests in 174 patients who received Kampo and in 231 patients who received no Kampo. The analyses was performed in relation to five factors, including age, clinical stage, concurrent chemotherapy, maintenance chemotherapy and maintenance immunotherapy. In all parameters, Kampo did improve the patient prognosis. The adjuvant therapy did not improve the clinical prognosis in both treatment groups.

Table 4. Univariate analyses of 5-year overall survival

Treatment	with Kampo (174 patients)			without Kampo (231 patients)		
Factors	No. of pts.	5-year survival rate	Breslow-Gehan-Wilcoxon p-value	No. of pts.	5-year survival rate	Breslow-Gehan-Wilcoxon p-value
Age			0.5935			0.045
<65 years old	64	65.6%		83	39.8%	
65 years old >=	110	70.8%		148	51.4%	
Clinical stage			0.0217			<0.0001
I,II	73	80.7%		102	67.6%	
III,IV	101	60.4%		129	31.0%	
Concurrent chemotherapy			0.025			0.0041
with	40	52.5%		32	28.1%	
without	74	72.8%		128	52,3%	
Maintenance chemotherapy			0.6584			0.3603
with	60	75.0%		71	45.1%	
without	74	72.8%		128	52,3%	
Maintenance immunotherapy			0.4393			0.2970
with	125	69.5%		110	51.8%	
without	49	67.3%		121	43.0%	

DISCUSSION

In recent years, dramatic advances in molecular biology have made it possible to analyze complex physioprotective systems at the molecular level. It is now important that we utilize this technology both in accurately assessing Kampo medicine from the viewpoint of modern science and also in developing new clinical applications for these products.

Kampo medicine has its roots in Chinese philosophy, as that it differs profoundly from Western medicine. Theories incorporating the principles of Yin and Yang and the five elements present a type of universalism in which everything is considered in relationship to everything else. The world represents one universe. Each human body is also a universe, containing within it the smaller universe of the organs including the liver, heart, spleen, lung and kidney. Everything has both a Yin and Tang aspect, and these aspects repeatedly oppose and are integrated with each other, so that the universe operates through cycles of growth and decay, according to the national philosophy presented by the Book of Divination (24).

Western medicine has its basis in science. Its orientation is mechanical, statistical and dualistic, with emphasis on local pathophysiology and the therapeutic focus is on the elimination of pathologic factors. Kampo medicine has its basis in universalism, and is humanistic, individualized, and monistic in its approach. The therapeutic focus is primarily on the functioning of the body, to increase the body's natural healing powers against outside factors. This treatment system also has as its objective the multifaceted regulation and optimization of physiologic functions.

A combination of Chinese and Western medicine began to be practiced in Japan from the 1950s. This new form of medicine, which combined the rich legacy of thousands of years of Kampo medical practice with the penetrating of modern medicine, began to develop rapidly beginning in the 1980s. Previous to that, we had already theorized that a new form of cancer treatment could be developed based on this combination of Chinese and Western medicine theory. Such treatment would utilize the powerful tools of Western medicine, such as surgery, radiation, and anticancer drugs, to directly combat cancer, but these treatments would be combined with restorative techniques specific to Kampo medicine which would replenish lost vitality and build up the natural healing powers of the body. There would also be concomitant use of BRM and other similar tools from Western medicine. By utilizing the strengths of both Western and Kampo medicine, this treatment method should provide optimal cancer therapy.

Our many years of experience with Kampo indicate that it is inappropriate to evaluate these products on the same scale as used to measure the clinical effectiveness of Western medicine. However, progress has been made in recent years on immu-

nologic analysis of cancer patients (9), and the present report provides information on survival rates. Gradually, we are approaching the point where objective evaluation will be possible.

Initially we began the concomitant administration of Kampo with the objective of reducing side effects and improving the quality of life (QOL) of patients undergoing radiotherapy and chemotherapy. However, our analysis of these patients showed that Kampo also provided life-prolonging effects.

In our study, stratified by treatment method, results from the cases in stage II showed the 5, 10, and 15 years survival rate were 78.9%, 61.8% and 41.8% treated with Kampo and 66.7%, 42.8% and 23.3% treated without Kampo, respectively (Fig. 2). Results from the cases in stage III showed the 5, 10, and 15 year survival rate were 62.3%, 49.1% and 41.2% and 41,0%, 28.2% and 12.9%, respectively (Fig. 3). Results from the cases in stage IV showed the 5, 10, and 15 years survival rate were 53.1%, 36.5% and 16.7% and 20.3%, 11.9% and 2.0%, respectively (Fig. 4). There was statistically significant difference in each stage (stage II : $p=0.0063$, stage III : $p=0.0004$, stage IV : $p<0.0001$).

In Japan, various forms of chemotherapy have been tested in conjunction with radiotherapy with the objective of prolonging survival in patients with advanced cervical cancer. However, although these methods increase the local success rate of cancer treatment, they do little to prolong survival, and their use is reportedly accompanied by a higher incidence of side effect (14, 25).

Multivariate analysis on 405 patients in this study showed that concomitant chemotherapy was not a significant prognostic indicator of prolonged survival ($p=0.4934$). Stage and concomitant Kampo therapy, however, did emerge as a significant prognostic indicator ($p<0.0001$ and $p=0.0001$).

We feel sure that further clinical research will result in the development of new applications for Kampo preparation, and that a combination of Chinese and Western medicine will prove beneficial in the treatment of cancer in the 21st Century.

CONCLUSION

Modern cancer treatment, which involves surgery, radiation and chemotherapy, inflicts great suffering and requires stoic endurance on the part of the patients. Kampo was introduced into cancer therapy to improve patient QOL, but has also been found therapeutically useful in itself. The results of our study indicate that concomitant Kampo has a significant positive effect on survival time.

We expect that cancer treatment in the 21st Century will maximize the patient's own natural healing abilities, and that concepts will be changed and further efforts will be made to decrease the difficulties of cancer therapy for the patient.

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