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In Vitro Radiosensitization of Flavopiridol Did Not Translated into *In Vivo* Radiosensitization

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Purpose: Flavopiridol enhanced radiation-induced apoptosis of cancer cells in our previous *in vitro* study. The purpose of this study was to assess if flavopiridol could enhance the radioresponse of mouse mammary tumors *in vivo*.

Materials and Methods: Balb/c mice bearing EMT-6 murine mammary carcinoma were treated with flavopiridol only, radiation only, or both for 7 days. Flavopiridol was administered 2.5 mg/kg twice a day intraperitoneally (IP). Radiation was delivered at a 4 Gy/fraction at 24-h intervals for a total dose of 28 Gy. Tumor volume was measured and compared among the different treatment groups to evaluate the *in vivo* radiosensitizing effect of flavopiridol. Tumors were removed from the mice 20 days after treatment, and TUNEL and Immunohistochemical stainings were performed.

Results: Significant tumor growth delay was observed in the radiation only and combined treatment groups, when compared with the control group. However, there was no significant difference between the tumor growth curves of the control and flavopiridol only group or between the radiation only and combination treatment group. Apoptotic cells of different treatment groups were detected by terminal deoxynucleotidyl transferase-medicated nick end labeling (TUNEL) staining. The expressions of Ku70 in tumor tissues from the different groups were analyzed by immunohistochemistry. Similarly, no significant difference was found between the apoptotic rate or Ku70 expression among the different treatment groups.

Conclusion: Flavopiridol did not show evidence of enhancing the radioresponse of mouse mammary tumors in this study.

Key Words: Flavopiridol, Radiation, Radiosensitization

Introduction

Flavopiridol is a synthetic flavonoid that was originally identified as a cyclin-dependent kinases (CDKs) inhibitor.[1~3] It induces growth arrest at either the G1 and/or G2 phase of the cell cycle in numerous cell lines by acting as a competitive binding agent for the ATP-binding site of CDK.[4] It has also been shown to have anticancer effects through inducing apoptosis and inhibiting angiogenesis of cancer cells.[5,6]

Flavopiridol potentiated the chemotherapy effects when it was combined with chemotherapeutic agent in many *in vitro* and *in vivo* studies.[7,8] Accordingly, flavopiridol has also been investigated of its potential role as a radiosensitizer in various cancer cells.[9~11]

Our previous study demonstrated that flavopiridol enhanced radiosensitivity of human uterine cervical, laryngeal and lung cancer cell lines (HeLa, AMC-HN3 and NCI-H460).[12,13] Flavopiridol enhanced the cell-killing effect of radiation through increasing radiation-induced apoptosis. The results of flow cytometry showed that sub-G1 fraction of cells were significantly increased in combination treatment group compared with that of radiation alone or flavopiridol alone treatment group. Western blotting also showed increased expression of cleaved caspase-3 and cleaved poly (ADP)

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ribose polymerase (PARP) expression in combination treatment group compared with that of radiation alone or flavopiridol alone treatment group.

DNA-dependent protein kinase plays a major role in the repair of double-strand breaks and is consisted of a regulatory subunit (Ku70 and Ku80 heterodimer) and catalytic subunit.[14] It has been shown that the suppression of Ku70 result in increased radiosensitivity in different type of malignancies.[15] Raju et al.[9] observed that flavopiridol treatment of murine ovarian cancer cells resulted in decreased levels of Ku70 and Ku86 proteins and suggested that inhibition of DNA damage repair may be a mechanism by which flavopiridol enhances the cancer cell radiosensitivity.

In this study, we examined whether flavopiridol potentiates radioresponse of *in vivo* mouse mammary tumor models and how it works.

Materials and Methods

1. *In vivo* tumor model

Male 5-week old Balb/c mice were used in this study. The animals were maintained in facilities approved by the Korean Food and Drug Administraion and in accordance with current regulations and standards of the Institutional Animal Care and Use Committee of Seoul National University. 5×10^5 EMT-6 cells (American Tissue Culture Collection, Manassas, VA, USA) were injected subcutaneously into the right hind leg of the mice. Treatment of tumor with flavopiridol and/or radiation was initiated when the tumors had grown to 8 mm in diameter.

2. Measurement of tumor volume

Flavopiridol was kindly provided by Aventis Pharmaceuticals (Bridgewater, NJ, USA) as a pure powder. The drug was prepared in 5% glucose water. 2.5 mg/kg of flavopiridol was injected to the mice intraperitoneally twice a day (9:00 am and 5:00 pm) for 7 days. This dose schedule was selected because it was proven to be most effective in the previous preclinical study.[16] Fractionated dose of radiation (4 Gy daily) was delivered with linear accelerator (Clinac 4/100, Varian, Palo Alto, CA, USA) for 7 days. The mice were randomized into 4 groups: control, flavopiridol alone, radiation alone, and combination of flavopiridol and radiation group. Flavopiridol and radiation was delivered on the same day in combination group. For combination treatment, the second dose of twice-a-day flavopiridol injection was given about 30 minutes after irradiation because the most obvious radiosensitizing effect of flavopiridol was observed when flavopiridol was administered following irradiation in our previous study.[12]

Tumors were measured three times a week manually, using a digital vernier caliper. Tumor volume was calculated according to the formula $1/2\times\text{length}\times\text{width}^2$. Mice from each group were sacrificed at 0, 3, 10, 15, and 20 days after treatment to provide tumor tissues for immunohistochemistry. We repeated the same experiment two times independently.

3. TUNEL assay

Apoptosis was assessed by the TUNEL method using the ApopTag Peroxidase In Situ Apoptosis Detection Kit (Chemicon, Temecula, CA, USA) according to the manufacturers instructions with minor modifications. Tumors for TUNEL were taken at day 10, 3 hours after irradiation or flavopiridol treatment. Sections of paraffin block of mice tumor tissue were deparaffinized in xylene and rehydrated in a graded concentration of ethanol and then in distilled water. They were then pretreated with proteinase K (20 μg/mL) for 15 minutes at room temperature and rinsed. Sections were incubated in 3% H_2O_2 for 5 minutes at room temperature. Equilibration buffer was applied on each sections for 20 seconds and sections were incubated with terminal deoxynucleotidyl transferase (TdT) enzyme for 1 hour at 37°C. The sections were rinsed in stop/wash buffer and incubated with anti-digoxigene peroxidase conjugate at room temperature for 30 minutes. For staining, the sections were incubated with diaminobenzidine (DAB) for 5 minutes. After staining and washing, the counterstaining was done with methyl green for 10 minutes. Apoptotic and nonapoptotic cells were counted in multiple randomly selected fields, and data were presented as percentage of apoptotic cells.

4. Immunohistochemistry (IHC)

Ku70 immunohistochemistry was carried out using the Cap-Plus™ Detection Kit (Zymed, San Francisco, CA, USA). Mice from each group were sacrificed at 0, 3, 10, 15, and 20 days after treatment to provide tumor tissues for immunohistochemistry. Five-micrometer-thick paraffin-embedded

tumor sections were cut, deparaffinized and rehydrated through graded alcohol series. Staining was performed with Ku70 antibody (Santa Cruz Biotechnology, Santa Cruz, CA, USA) at a dilution of 1 : 200 after microwave antigen retrieval. After incubation at 4°C for overnight, sections were incubated with a second biotinylated antibody for 20 minutes. After washing, sections were treated with streptavidin-HRP-reagent, incubated with DAB and counterstained with hematoxylin. Sections of human breast tumor were used as a positive control, and a negative control without primary antibody was prepared on each case. A single pathologist reviewed the IHC results. The number of cells in tumor samples stained positive for Ku70 was determined by scoring 10 microscopic fields of 100 tumor cells each, without prior knowledge of radiosensitivity or treatment outcome, and determining the percentages of cells that were positive for Ku70 expression. The values are expressed as Ku70 index (percentage of Ku 70-positive cells).

5. Statistical analysis

Statistical analysis was performed using Mixed Model Analysis and Tukey-Kramer test. A p-value of less than 0.05 was considered to be statistically significant.

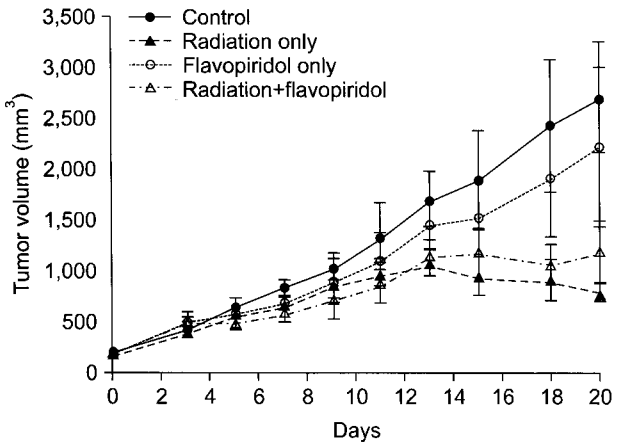

Fig. 1. Growth of EMT-6 tumors. EMT-6 breast carcinoma cells were injected into the musculature of the right proximal hind leg of male Balb/c mouse. When tumors reached a diameter of 8 mm, mice were randomly assigned to control, flavopiridol (2.5 mg/kg) only, radiation (4 Gy) only or combination of flavopiridol and radiation group and treated for 7 days. Data shown are mean±standard deviations from two independent experiments.

Results

To determine whether flavopiridol improves tumor response to radiation, we performed tumor growth delay analyses using the mammary tumor models of mice. EMT-6 cells were injected into the Balb/c mice to form solid tumors and randomized into four groups. The animals were monitored for tumor growth for 20 days. The result of tumor growth delay assay is presented in Fig. 1. When compared with control group, radiation alone and combination treatment group resulted in a detectable growth delay but the growth rate of flavopiridol alone group was the same as that of control group.

The tumor size measurement was done for 10 times during the 20 days of observation period. The mean and standard deviations of tumor size of each group at each measurement time are presented in Table 1. The least square mean values

Table 1. The Tumor Size of Each Treatment Group at Each Measurement Time

Measurement time	A (control)		B (radiation only)		C (flavopiridol only)		D (radiation+flavopiridol)	
	No.	Mean±SD*	No.	Mean±SD	No.	Mean±SD	No.	Mean±SD
1	15	383.3±362.6	14	302.4±172.0	15	292.5±154.8	14	302.9±183.6
2	14	543.9±263.4	13	515.8±199.7	15	557.5±178.0	13	556.3±208.1
3	12	715.5±241.7	12	618.2±156.1	14	604.1±192.5	12	504.6±137.2
4	11	911.3±329.5	11	713.0±172.6	13	783.3±268.9	11	587.5±217.3
5	11	1,128.8±323.4	11	902.0±220.0	13	1,002.4±299.1	11	764.2±210.5
6	11	1,409.8±460.9	11	987.0±243.0	13	1,205.1±319.0	11	923.7±210.4
7	10	1,884.2±553.7	10	1,023.6±269.3	12	1,584.2±375.2	10	1,151.9±244.8
8	10	2,105.6±675.5	10	859.9±287.8	12	1,732.2±490.8	10	1,243.8±324.8
9	9	2,672.1±823.8	9	910.2±413.7	11	2,248.4±670.2	9	1,268.5±390.3
10	5	2,694.8±551.6	4	787.6±94.6	6	2,217.3±780.2	4	1,175.1±310.6

*standard deviation.

Table 2. Pairwise Comparison of Least Square Mean of Tumor Size

	8th measurement		9th measurement		10th measurement	
	Lsmean*	p-value	Lsmean	p-value	Lsmean	p-value
A-B	1,245.7	<0.0001	1,761.8	<0.0001	1,907.2	0.0006
A-C	373.4	0.2668	423.6	0.4177	477.4	0.5026
A-D	861.8	0.0012	1,403.5	0.0001	1,519.7	0.0047
B-C	−872.3	0.0006	−1,338.2	0.0001	−1429.7	0.0056
B-D	−383.9	0.2798	−358.3	0.5982	−387.5	0.7561
C-D	488.4	0.0906	979.9	0.0054	1,042.3	0.0463

*least-squares mean.

of tumor size at 8th to 10th measurement were estimated using mixed model. And the pairwise comparisons of the least square mean of tumor size were done using Tukey-Kramer test (Table 2). There were significant differences between the tumor sizes of radiation only group (B) and control group (A), but no differences between those of flavopiridol only group (C) and control group (A). The differences between the tumor size of the flavopiridol only group (C) and combination treatment group (D) were significant, but those of radiation only group (B) and combination treatment group (D) were not significant. Therefore, flavopiridol had no tumor growth delay

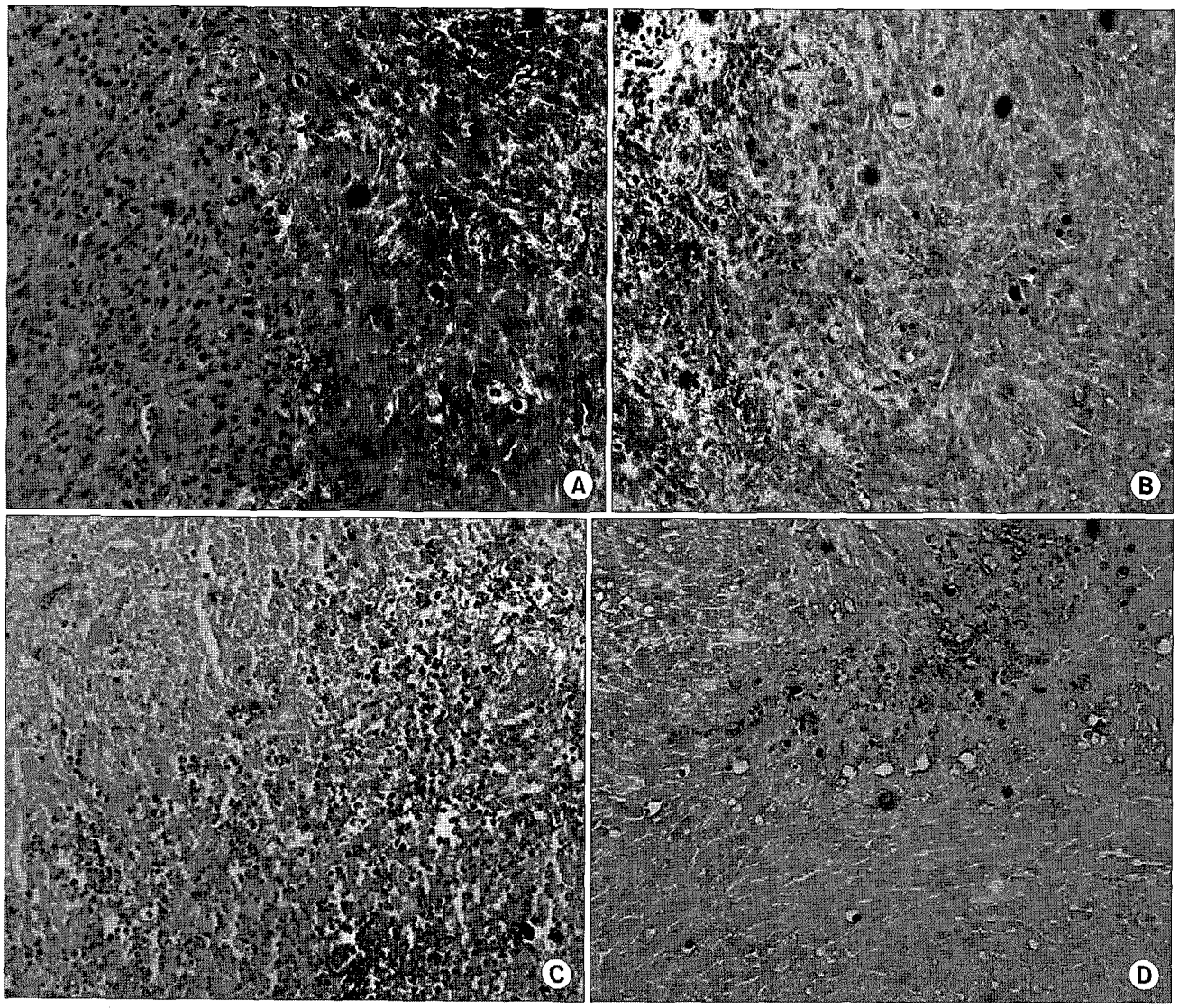

Fig. 2. TUNEL staining of tumors that have undergone different treatments (A, control; B, flavopiridol only; C, radiation only; D, radiation+flavopiridol; ×200). Tumors were taken at day 10 and TUNEL assays were done as described in Materials and Methods. Results shown are representative of two independent experiments. TUNEL: terminal deoxynucleotidyl transferase-medicated nick end labeling.

effect by itself and neither did it enhance the tumor growth delay effect of radiation.

To determine whether flavopiridol enhances radiation-induced apoptosis *in vivo*, TUNEL staining of apoptotic tumor cells was studied. Apoptosis rate of tumors treated by flavopiridol only group was not significantly different from that of control group. The percentage of apoptotic cells was 2% for both control and flavopiridol only groups. We could not find any relationship between apoptosis rate and treatement (Fig. 2).

Ku70 immunohistochemical staining demonstrated nuclear reaction product. The percentage of cells expressing Ku70 was found to be 40%, 40%, 20%, and 40% for control, flavopiridol only, radiation only, and combination group, respectively. There was no significant difference of Ku70 expression among the different treatment groups (Fig. 3). These analyses showed that flavopiridol did not inhibit cellular DNA damage repair.

Discussion and Conclusion

Cell cycle progression in mammalian cells is controlled by

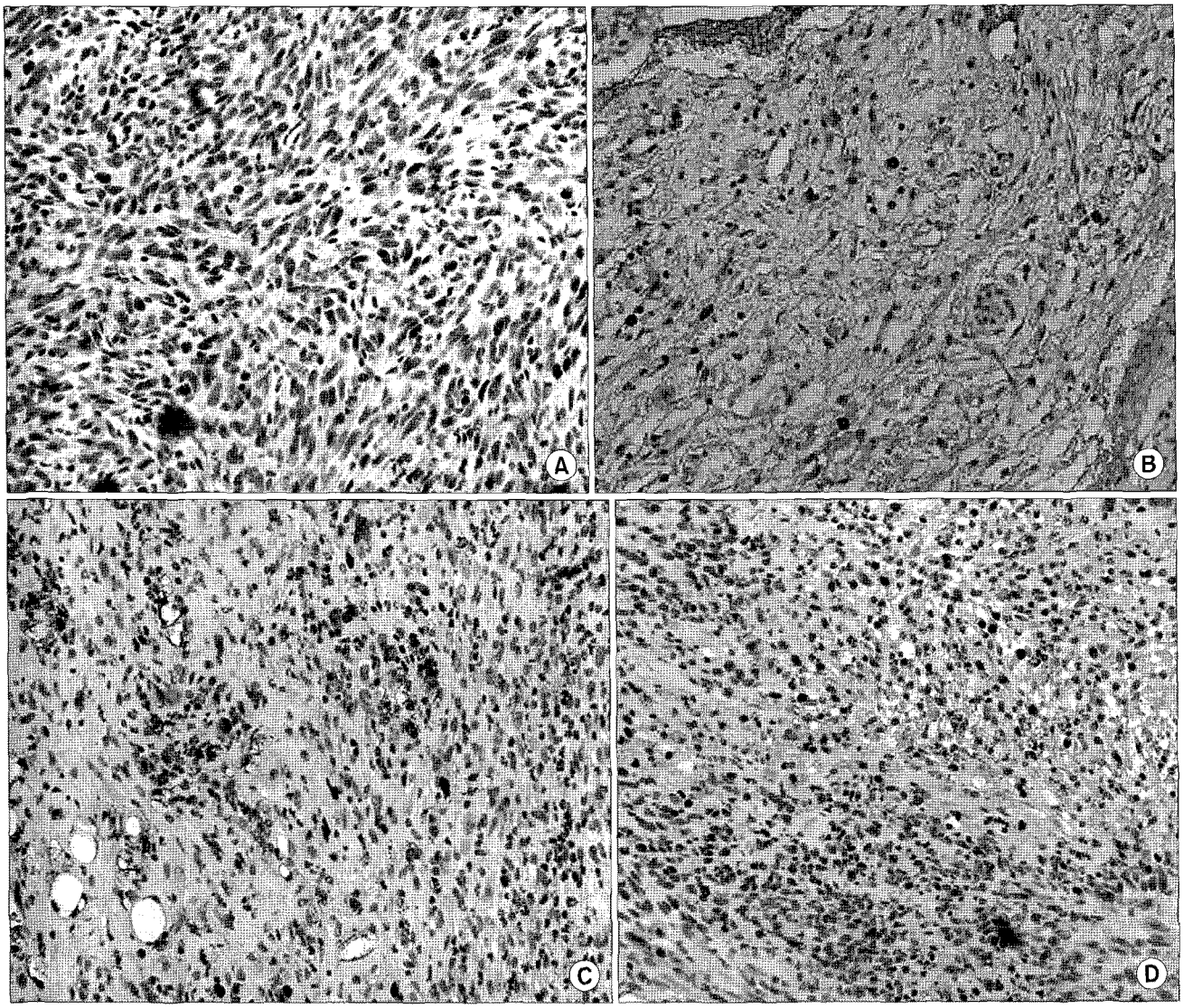

Fig. 3. Ku 70 immunostaing of tumors that have undergone different treatments (A, control; B, flavopiridol only; C, radiation only; D, radiation+flavopiridol; ×200). Tumors were obtained at day 20 and immunohistochemistry for Ku70 was done as described in Materials and Methods. Results shown are representative of two independent experiments.

both cyclins and cyclin-dependent kinases. In cancer cells, cell cycle-regulatory proteins are frequently expressed abnormally.[17,18] Targeting these molecules may, in some cases, improve cancer cells' responses to radiotherapy. In this regard, flavopiridol, recently identified as a potential drug candidate for cancer treatment, has been demonstrated to behave as a potent and remarkably specific cdk inhibitor.[5,19]

Flavopiridol had radiosensitizing effect on human uterine cervix cancer, head and neck cancer, and lung cancer cell lines in our previous works.[12,13] In the present study, we used mouse breast cancer model to investigate the value of flavopiridol as a radiosensitizer *in vivo*.

Flavopiridol had no effect on tumor growth delay. Tumor growth inhibition caused by combination treatment was not greater than that by radiation alone. This data suggest that flavopiridol had no radiosensitizing effect *in vivo*.

Apoptosis is a complex biological process in which the activation of one or more apoptotic pathways leads to a series of biochemical events ultimately resulting in cell destruction. Flavopiridol has been reported to enhance the radiation-induced apoptosis in malignant glioma, gastric, colon, lung and esophageal cancer cells.[10,11,20] In our previous *in vitro* study, increased apoptotic rate was observed in combination treatment group compared with that of radiation or flavopiridol alone group.[13] In this *in vivo* study, apoptosis was confirmed by TUNEL assay and there was no difference of apoptosis rate according to the type of treatment. Although TUNEL assay is useful method for detecting apoptosis with intact tissue sections, there are some limitations. TUNEL assay is not specific for detecting apoptosis and apoptotic cells *in vivo* can be removed from tissue by phagocytic cells.[21] Therefore, we think the negative result from TUNEL assay should be interpreted carefully.

Ku70 is a DNA double strand breaks repair enzyme and it has been shown that Ku70 deficiency results in increased ionizing radiosensitivity in animal models.[22,23] Some investigators suggested that flavopiridol increase the radiosensitivity of cancer cells through inhibition of DNA damage repair.[9,24] But the present study could not demonstrate any correlation between the Ku70 expression and flavopiridol treatment.

Recently, Hara et al.[25] suggested that flavopiridol enhances the cytotoxic effect of radiation in radioresistant tumor cells that harbor p53 dysfunction or Bcl-2 overexpression. They used a human glioma cell line (A172/mp53) stably transfected with a plasmid containing mutated p53 and a human cervical cancer cell line (HeLa/bcl-2) transfected with a bcl-2 expression plasmid. Flavopiridol increased the cytotoxic effects of radiation in both transfected cell lines through inhibiting DNA damage repair. But it didn't show radiosensitizing effect in their parental wild-type cell lines.

We think such studies investigating the relationship between genetic changes of the tumor and radiosensizing effect of flavopiridol should be carried out further. We didn't check the p53 or bcl-2 status in our tumor models but it may be related with radiosensitizing effect of flavopiridol. Mason et al.[16] observed that flavopiridol enhanced radioresponse of mouse tumors. They used three transplantable mouse tumors: mammary carcinoma (MCa-29), ovarian carcinoma (OCa-1), and a lymphoma (Ly-TH). Fractionated radiation was given to MCa-29 tumors and flavopiridol enhanced tumor response to radiation. The different result from our study may be due to the different genetic characteristics of tumors.

In conclusion, flavopiridol didn't increased radioresponse of mouse mammary tumor *in vivo*. Neither flavopiridol had any effect on radiation-induced apoptosis or DNA damage repair in this mouse tumor model. But more investigations on the genetic characteristics of tumor and radiosensitizing effect of flavopiridol are required in the future.

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국문초록

마우스를 이용한 생체내 실험에서의 플라보피리돌의 방사선민감화 효과

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김 수 지

목 적: 이전의 암세포주를 이용한 실험실내 연구에서 플라보피리돌은 암세포의 방사선에 의한 아포토시스를 증가시키는 것을 알 수 있었다. 이번 연구에서는 마우스를 이용한 생체내 실험에서 플라보피리돌의 방사선민감화 효과를 알아보고자 하였다.

대상 및 방법: 마우스 유방암 세포주인 EMT-6를 Balb/c 마우스에 피하주사하여 종양을 만든 후 플라보피리돌 단독 치료군, 방사선 단독 치료군, 방사선과 플라보피리돌 병합 치료군 및 대조군으로 나누어 종양의 성장 속도를 비교하였다. 플라보피리돌은 2.5 mg/kg을 하루 2회 복강내에 주사하였고, 방사선은 1일 1회, 회당 4 Gy를 조사하여 총 28 Gy를 조사하였다. 각 치료군에서의 종양 성장 곡선을 구하여 비교하였다. 마우스로부터 채취한 종양으로 파라핀 절편을 만들어 TUNEL 및 면역조직화학염색을 시행하였다.

결 과: 종양 성장을 비교하였을 때 대조군보다 방사선 단독 치료군과 방사선과 플라보피리돌 병합 치료군에서 종양 성장이 지연되는 것을 볼 수 있었다. 그러나 대조군과 플라보피리돌 단독 치료군 사이에서는 종양 성장에 차이가 없었고, 방사선 단독 치료군과 방사선과 플라보피리돌 병합 치료군 사이에서도 차이가 없었다. TUNEL 염색으로 아포토시스율을 비교했을 때 각 치료군 사이에 차이가 없었으며, 면역조직화학염색으로 Ku70 발현을 비교했을 때에도 각 치료군 사이에 차이가 없었다.

결 론: 플라보피리돌은 마우스 유방암 모델에서 방사선민감화 효과를 나타내지 않았다.

핵심용어: 플라보피리돌, 방사선치료, 방사선민감화