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Chemosensitivity Testing of Gynecologic Tumors to Chemotherapeutic Agents by the Subrenal Capsule Tumor Implant Assay[1,2]

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= Abstract =Subrenal capsule assay (SRCA) is a promising method of "*in vivo*" chemosensitivity test. We planned the laboratory procedure of SRCA in order to make an animal model of *in vivo* chemosensitivity test which can be used for the gynecologic cancers.

The 6-day subrenal capsule assays were performed with several gynecologic malignancies. Fresh tumor fragments of cervical cancer, ovarian cancer, endometrial cancer, sarcoma, and choriocarcinoma were implanted as 1 × 1 × 1 mm fragments under the renal capsule of immunocompetent female adult mice and tested against several chemotherapeutic drugs or their combinations.

In this study, we could show the variations in growth rates of the xenografts under the renal capsule. This fact seems to reflect the differences of the growth potentials as well as the heterogeneity of the cell population comprising each human tumor. An average of 69.3% of tumors showed positive growth and 10.6% demonstrated no measurable change, but 20.0% showed partial regression in size. The evaluable assay rate of this study was over 90.5%.

The response rates of 19 cervical carcinomas, 2 ovarian carcinomas, 1 endometrial carcinoma, 1 sarcoma, and 1 choriocarcinoma to several chemotherapeutic agents and their combinations were determined. Response rates varied from 0% (0/3) to adriamycin to 85.7% (6/7) to epirubicin plus cis-platin in cervical carcinoma (cf: 75.0% (9/12) to cis-platin, 42.9% (3/7) to cyclophosphamide, 40.0% (4/10) to 5-fluorouracil, and 66.7% (4/6) to bleomycin).

A total of 13 clinical correlations of SRCA with clinical outcome were possible in the prospective study, and the overall predictive accuracy of the SRCA in our study was 84.6%.

The SRCA is considered as a reliable *in vivo* clinical test to predict the effectiveness of drugs against a tumor in an individual patient.

Key words: ***Subrenal capsule assay, in vivo test, Gynecologic malignancies, Predictive assay, Chemosensitivity***

INTRODUCTION

Patients with cancers are frequently treated with the chemotherapeutic agents. But the chemotherapeutic agents are chosen on the basis of the statistical evaluation of clinical studies involving many patients and physician preferences, not on the responsiveness of individual tumors to chemotherapeutic agents because of the lack of a suitable tumor sensitivity test. Thus several chemosensitivity testings have been tried for the prediction of the chemosensitivity of malignant tumors.

For example, the double-layer-soft-agar method was developed (Hamburger and Salmon 1977). This technique is commonly referred to as the "clonogenic assay" now. But this assay has current

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several problems, including low plating efficiencies, nonstandardized drug concentrations, and methods of exposure, existence of nonstandardized criteria for *in vitro* sensitivity, and methods of colony counting (Bertelsen *et al.* 1984). Furthermore, the *in vitro* tissue culture systems bypass the normal metabolic processing capacity of the animal and therefore might be inaccurate to reflect the responsiveness of whole animal to chemotherapeutic agents. Many tumors cannot grow easily in tissue culture and up to 75% of tumor specimens may be unevaluable due to insufficient growth of control cultures (Von Hoff *et al.* 1981; Mattox *et al.* 1984).

So the subrenal capsule assay is adapted for the "*in vivo*" chemosensitivity testing. This assay is a precise technique which makes it possible to quantify minute changes in the size of human tumor xenografts implanted into the sub-capsular region of the kidney in normal immunocompetent mice (Hunter *et al.* 1982). The subrenal capsule assay is the reliable technique for predicting clinical response to chemotherapy. This assay is relatively simple to perform and results are available within a week, so the test is quick enough to benefit the patient. Also, the relation between the efficacy of cytostatic treatment and its toxicity may be evaluated in this test.

Thus for the first time in Korea, we planned the laboratory procedure of SRCA as an animal model of *in vivo* chemosensitivity test which can be used not only for gynecologic malignancies but also for other malignancies. This report describes the preliminary results of our pilot study with subrenal capsule assay.

MATERIALS AND METHODS

Originally the subrenal capsule assay was performed with athymic mice to aid in new drug screening (Bogden *et al.* 1978), but it has been modified to handle fresh human tumor specimens (Bogden *et al.* 1979; Bogden *et al.* 1980).

Tumor specimens were obtained at the time of operation from patients, most of whom had advanced malignancies who were being treated in the Gynecologic Department of Seoul National University Hospital.

The obtained tumor specimens were sectioned into about 10 mm^3 pieces and immediately placed into sterile Minimum Essential Medium (MEM, Irvine Scientific, USA) and stored at 4°C in refrigerator until the assays were performed. We performed the assay as early as possible after the sampling of tumor specimen, usually within one day. Just before implantation of tumor, viability test of the tumor specimen was done with trypan blue. Viability varied from 15% to 90% in our assays. After the viability test, tumor tissue was cleaned of blood, necrotic tissue, and fat, and then placed in a dish of sterile cold MEM. The tumor tissue was diced into nearly 1 mm × 1 mm × 1 mm pieces with No. 10 blades. While preparing the fragments of the tumor, young female adult BALB-C mice weighing 18-25 gm were anesthetized with intraperitoneal injection of 0.22 M chloral hydrate solution (Yakuri Pure Chemicals Co., LTD, Osaka, Japan, Dose; 0.012 mg/gm of body weight), and then shaved on left dorsal area, weighed and numbered. An 5-8 mm skin incision was made on the left dorsum and the left kidney was exteriorized. Then a small nick was made in the kidney capsule with a No. 11 surgical blade. A piece of tumor fragment was inserted into subcapsular region using a 20-gauge needle with trocar. The implanted tumor fragment was measured in two dimension with an ocular microunits (OMU; 10 OMU = 1.0 mm). After measuring the size of implant, the kidney was returned into the abdominal cavity and the wound was closed using a stapler. Animals were allowed to recover from surgery in a cage under the heat lamp. A minimum of 4 control animals and 4 or more animals per chemotherapeutic drug tested were used. The chemotherapy was initiated the next day. The selected single chemotherapeutic agent or combinations of them were injected into peritoneal cavity daily for 5 days while the control mice received saline injection. The combination therapies were administered as full doses of each separate therapy in all cases. The chemotherapeutic agents used and concentrations injected are listed in Table 1.

The mice were sacrificed by cervical dislocation on the day after the last chemotherapy. Then the tumor-bearing kidneys were exposed and the tumor implants measured once again *in situ*. The average change in tumor size of the length and width measurements is calculated for each animal. These measured values are then averaged to give the change in tumor size, or △ TS, for each group of animals. A theoretical weight of the tumor can be calculated using the formula for the volume of an ellipsoid, $(L \times W^2)/2$ (Hunter *et al.* 1982). Percentage regression of tumor is calculated on the basis of initial tumor weight of the treated test group.

Standard criteria of clinical tumor response and regression (Miller *et al.* 1981) were used in the

Table 1. Drugs tested in the SRC assay: dosage and combination therapies

Code	Chemical name	Mouse dose	
		mg/ml[a]	mg/kg
CDDP	Cis-platin	0.4	2.0
CTX	Cyclophosphamide	10.4	50.0
ADR	Doxorubicin	0.8	4.0
5-FU	5-Fluorouracil	10.0	50.0
MTX	Methotrexate	0.8	4.0
VCR	Vincristine sulfate	0.05	1.0
Epirubicin	4′-Epi-Doxorubicin Hydrochloride	0.6	3.0
BLEO	Bleomycin	0.6	3.0
CAP	CTX + ADR + CDDP	Days 1 — 5	
VAC	VCR + AcD + CTX	Days 1 — 5	

a; Mice received 0.1 ml of this concentration per day for 5 days.

Table 2. Growth of human gynecologic tumors implanted as first transplant generation xenografts under the renal capsule of BALB-C mice[a]

Histologic type	Total Xenografts	Individual Xenografts		
		Positive growth	No measurable change	Partial regression
Ovarian	4	3(75%)[b]	0(0%)	1(25%)
Endometrial	4	3(75%)	0(0%)	1(25%)
Cervical	63	42(66.7%)	8(12.7%)	13(20.6%)
Sarcoma	3	3(100%)	0(0%)	0(0%)
Choriocarcinoma	1	1(100%)	0(0%)	0(0%)
Total	75	52(69.3%)	8(10.6%)	15(20.0%)

a; Tissue implanted include all surgical specimens
b; Percentages shown in parentheses

assessment of the clinical response to chemotherapy.

RESULTS

Some tumor implants grew easily, but some tumors grew so slowly that no change in size from the initial specimen was measurable, and some xenografts containing necrotic elements showed a decrease in size. In other words, the fresh tumor fragments implanted under the renal capsule showed variable growth rates. These variable growth rates appear to reflect both the growth potential characteristic of each tumor type as well as the heterogeneity of the cell populations comprising each tumor specimens (Hunter *et al.* 1982).

When each piece of tumor implanted in an untreated mouse is considered as a separate transplant, the 75 xenografts from five major types of gynecologic malignancies have been implanted (Table 2). An average of 69.3% have shown positive growth and 10.6% demonstrated no measurable change, but 20.0% showed partial regression in size. The proportion of xenografts showing positive or no growth is the same for ovarian and endometrial carcinomas, and also the same for sarcoma and choriocarcinoma. But the proportion of xenografts showing positive growth was somewhat low for cervical carcinoma. If tumors which regress are disregarded, then the growth potential of the 5 tumor types can be assessed by the average growth of the tumor pieces in the 6-day period in the untreated mice.

Table 3. Numbers of evaluable assays obtained with human gynecologic tumors in the subrenal capsule assay

Histologic type	Evaluable[a]/total	Percentage of assay evaluable
Ovarian	2/ 2	100%
Endometrial	1/ 1	100%
Cervical	19/21	90.5%
Sarcoma	1/ 1	100%
Choriocarcinoma	1/ 1	100%

a; Criterion for evaluability = control growth $\triangle$ TS $\geq -$ 0.5 OMU

The number of evaluable assays obtained with gynecologic tumors in the subrenal capsule assay was high and ranged from 90.5% to 100% as shown in Table 3. The criterion for evaluability of the subrenal capsule assay has been defined as stable or positive growth in the untreated controls, that is, the average change in tumor size $\geq -$ 0.5 OMU (Hunter *et al.* 1982).

The response rates of various human gynecologic neoplasms to chemotherapeutic agents or their combinations have been obtained for 2 ovarian, 1 endometrial, 19 cervical carcinomas, 1 sarcoma, and 1 choriocarcinoma (Table 4). A tumor was considered to be sensitive to drug if the average regression $\geq$ 25% (Hunter *et al.* 1982). The response rates in the subrenal capsule assay varied from 0% to 100% as shown in Table 4.

The responses to chemotherapy for each tumor specimens are shown in Table 5 and 6. As shown in these tables, some tumors were sensitive and others unresponsive to drugs tested. The responses of individual cervical carcinoma show the heterogeneity of tumor responses when individual carcinoma show the heterogeneity of tumor responses when individual cervical tumors are listed (Table 5). The cervical tumor responses for VCR or 5-FU plus cis-platin were both positive (both 1/1), but these response rates were not reliable because the number of the treated test group was too small. The response rates of cervical tumors were 85.7% to epirubicin plus cis-platin, 75.0% to cis-platin, 66.7% to bleomycin, 42.9% to cytoxan, and 40.0% to 5-FU in orders. So the combination of epirubicin and cis-platin or cis-platin as a single agent showed relatively high response rates. Although the number of other gynecologic tumors were not enough in this study, those tumors also showed

Table 4. Comparison of the response rates of various neoplasms of the human female to clinically active chemotherapeutic agents (subrenal capsule assay)

Tumors	Number Tested	Chemotherapeutic agents (response rate)[a] (Responding/tested)											
		5-FU	CTX	CDDP	ADR	VCR	BLEO	MTX	VAC	CAP	5-FU + CDDP	Epirubicin + CDDP	Epi-rubicin
Ovarian	2	.	100(1/1)	0(0/1)	100(1/1)	.	.	.	.	100(2/2)	.	.	.
Endometrial	1	100(1/ 1)	0(0/1)	0(0/1)	0(0/1)	.	.	.	.	.	.	.	.
Cervical	19	40.0(4/10)	42.9(3/7)	75.0(9/12)	0(0/3)	100(1/1)	66.7(4/6)	.	.	.	100(1/1)	85.7(6/7)	50.0(1/2)
Sarcoma	1	.	.	.	.	.	.	.	100(1/1)	.	.	.	.
Chorioca.	1	.	.	0(0/1)	.	.	100(1/1)	100(1/1)	.	.	.	.	.

a: Positive response = tumor regression $\geq$ 25%
VAC: VCR + AcD + CTX
CAP: CTX + CDDP + ADR

Table 5. Responses of cervical tumors to chemotherapeutic agents in the subrenal capsule assay

Patient SRCA NO.	Response to chemotherapeutic agents[a]									Control growth (OMU)
	5-FU	CTX	BLEO	CDDP	VCR	ADR	5-FU+ CDDP	Epirubicin + CDDP	Epirubicin	
C— 2	−	−	−	+						+ 1.9
C— 3	+	−	+	+						+ 2.3
C— 4	−	+	+	−						+ 3.5
C— 5	−		+	+	+					+ 0.8
C— 6	+	−	−	+						− 0.3
C— 9	+	+	+	+						+ 0.1
C—11	−			+		−	+			+ 3.0
C—13	−	+		−		−				+ 2.0
C—14	−	−		+		−				+ 1.8
C—15				+						+ 0.6
C—15				+						+ 0.9
C—17								+		+ 0.3
C—19								+		− 0.5
C—20	+			−					+	+ 2.0
C—21								+		+ 0.7
C—22								+		+ 2.2
C—23								+		+ 0.1
C—24								−		+ 1.0
C—25								+	−	+ 0.9
Responding/ tested	4/10	3/7	4/6	9/12	1/1	0/3	1/1	6/7	1/2	
R.R(%)	40.0	42.9	66.7	75.0	100	0	100	85.7	50.0	

a; Positive response = tumor regression $\geq$ 25%
R.R; Response rate

individual variance of responses to chemotherapeutic agents in each other (Table 6).

We tried the SRCA/clinical response correlations in the prospective study including these gynecologic tumors. In our prospective study, a total of 13 clinical correlations were possible (9 cervical carcinomas, 2 ovarian carcinomas, 1 endometrial carcinoma, and 1 choriocarcinoma). Of the 9 clinically sensitive responses, the SRCA accurately predicted 8 or 88.9%. Of the 4 clinically resistant responses, the assay accurately predicted 3 or 75.0%. Thus the overall predictive accuracy of the SRCA in our study was 84.6% (Table 7).

DISCUSSION

For over 10 years, many clinical investigators have made considerable efforts to develop *in vivo* test that could accurately predict the chemosensitivity of a malignant tumor as the microbial culture and sensitivity assays (Bertelsen *et al.* 1984). A number of assay techniques have evolved including "clonogenic assay". The preliminary clinical experience with the stem cell clonogenic assay was encouraging. The overall accuracy of the test was reported to be greater than 75% with 85-92% for the prediction of clinical resistance to chemotherapy (Bertelsen *et al.* 1978). But the current problems in the assay methods include low plating efficiencies, nonstandardized drug concentrations and methods of exposure, existence of nonstandardized criteria for *in vitro* sensitivity, and methods of colony counting (Bertelsen *et al.* 1984). The major disadvantages of the clonogenic assay are the dismal cloning efficiency of about 0.001% (Von Hoff *et al.* 1981; Mattox *et al.* 1984), evaluable growth rates of 23% to 36% (Von Hoff *et al.* 1981; Mattox *et al.* 1984), the high incidence of bacterial and fungal contamination (Mattox *et al.* 1984), the long time necessary for evaluable clones to develop (Stratton *et al.* 1984), and the technical difficulties

Table 6. Responses of various gynecologic tumors other than cervical tumors to chemotherapeutic agents in the subrenal capsule assay

Patient SRCA NO.	Response to chemotherapeutic agents[a]								Control growth (OMU)
	BLEO	MTX	5-FU	CDDP	CTX	ADR	CAP	VAC	
C — 1 (Chorioca.)	+	+		−					+ 2.0
C — 10 (Ovarian ca.)				−	+	+	+		+ 0.5
C — 16 (Ovarian ca.)							+		+ 1.6
C — 12 (Endometrial ca.)			+	−	−	−			+ 3.1
C — 18 (Sarcoma)								+	+ 2.5

a; Positive response = tumor regression $\geq$ 25%

Table 7. SRCA/clinical response correlations[a]:prospective study

No. of correlations	S/S	S/R	R/R	R/S
13	8	1	3	1
Predictive of clinical sensitivity		8/9	(88.9%)	
Predictive of clinical resistance		3/4	(75.0%)	
Overall predictive accuracy		11/13	(84.6%)	

a: assay results/clinical outcome
S = drug sensitive R = drug resistant

of obtaining a single cell suspension (Stratton *et al.* 1984).

But there are several merits of the SRC assay. The use of fresh tumor fragments provides well preserved tissue permeability barriers for chemotherapeutic drug testing (Stratton *et al.* 1984). Also, drugs that need *in vivo* activation such as cyclophosphamide are evaluable in this *in vivo* assay· (Stratton *et al.* 1984). Conceptually intact cell-to-cell contact and spatial relationships considered to be important in predicting true drug activity can be afforded by SRC assay (Stratton *et al.* 1984). The SRC assay is technically simple and the results are available within a week allowing use of results in treatment of cancer patients.

Hunter *et al.* (1982) reported that an average of 60% showed positive growth and 11% demonstrated no measurable change in size of untreated tumors implanted. In present study, we obtained similiar positive growth (69.3%) and no measurable growth (10.6%). Tumors have the potential to grow in the subrenal capsule assay because of the rich blood supply to the subcapsular region. The small size of the tumor graft allows for diffusion of nutrients as well as test drugs into the explant without the lag time that would be required to develop a vascular supply. Many studies have shown that the increase in tumor size of untreated tumors is related to the mitotic activity as well as to the degree of tumor necrosis present in the surgical specimen (Hunter *et al.* 1982). Recent histologic studies by Reale *et al.* (1984) showed that (a) tumor histologic architecture is preserved in the explants out to day 6 in both immunocompetent and athymic nude mice; (b) host infiltrate of inflammatroy cells begin as early as day 3 and peak at day 10; (c) the extent of infiltration does not significantly affect tumor size up to and through day 6.

Levi *et al.* (1984) found that fresh explants of human tumor retain their proliferative and metabolic capacity at least 4 days after implantation under the renal capsule of immunocompetent mice. He also found that the mean tumor size from any tumor specimen did not differ between days 4 and 6. These observations suggest that the cellular infiltration is not artifactual to the extent that it precludes the validity of a simple tumor size parameter for evaluating drug effects. Furthemore, the immune system of the mice cannot reject the implant of tumor within such a short 6-day time frame (Hunter *et al.* 1982).

The response rate of gynecolgic tumors to che-

motherapeutic agent in SRC assay quite varied from 0% to 100% in this study. Hunter *et al.* (1982) also noted variable response rate from 6% to tamoxifen in cervical carcinoma to 80% to 5-FU in ovarian carcinoma. It is doubful whether these rates reflect clinical response rates when optimal doses and schedules are used for these chemotherapeutic agents of their combination in previously untreated patients with minimum tumor burdens.

Clinical correlations of the SRC assay with clinical outcome was surveyed prospectively in this study. 13 patients have received at least three courses of chemotherapy tested in the SRC assay. The patients with complete remession or partial remission for at least 4 months were categorized as sensitive to the chemotherapy. All other responses were categorized as resistant to the chemotherapy. The overall predictive accuracy (efficiency) of the SRC assay was 84.6% with 75% accuracy at predicting clinical resistance to chemotherapy and an evaluable tumor growth rate of greater than 90.5%. According to other data, the overall predictive accuracy of the SRC assay has been reported to be 85% with 90% accuracy at predicting clinical resistance to chemotherapy and an evaluable growth rate of greater than 86% (Griffin *et al.* 1983). Stratton *et al.* (1984) have reported predictive efficiency of 67% with 81% accuracy at predicting clinical resistance to chemotherapy and an evaluable tumor growth rate of 89%.

So, we can get a high evaluable tumor growth rate and a good overall predictive accuracy of the SRC assay in this study. We can complete the SRC assays in a short time frame. Thus the SRC assay is considered as an effective *in vivo* test in mice for a quick determining of the responsiveness of gynecologic tumor to the variable chemotherapeutic agents and clinically useful in determining the individualized treatment for the patients with cancer. However, there are several problems of SRCA to predict effectiveness of drugs. (1) The tissue penetration of the chemotherapeutic drug may be different in the human than it is in the mouse. (2) The dose of the drug that the patient receives may not be as optimal as that received by the mouse. (3) The patients' tumor might respond well to drug initially, but develop resistance during therapy as certain resistant subpopulations are selected.

Our SRC assays are currently ongoing, and the prospective clinical correlations of the SRC assays with clinical outcome will be studied continuously.

In summary, the SRC assay is a reliable *in vivo* clinical test to predict the effectiveness of drugs against a tumor in an individual patient, and we believe that the feasibility of this SRC assay will be validated by the good predictive accuracy of the assay in Korea.

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= 국문초록 =

신피막하 종양이식 분석법에 의한 부인과 악성종양의 화학감수성 검사에 관한 연구

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신피막하 종양이식 분석법은 *in vivo*의 조건에서 시행할수 있는 부인과 종양의 화학감수성검사 방법으로 최근 많은 관심을 끌고 있다.

저자들은 난소암 2예, 자궁내막암 1예, 자궁경부암 19예, 육종 1예, 융모상피암 1예를 자료로 하여 국내 최초로 신피막하 종양이식 분석법을 실시한 바 아래와 같은 결과를 얻었다.

1. 종양세포 생육성 (cell viability)은 15%-90%이었다.
2. 신피막하 종양이식 분석법의 분석가능율 (evaluable assay rate)은 90.5% 이상이었다.
3. 자궁경부암에 있어서 각각 adriamycin에 0% (0/3), epirubicin과 cis-platin의 복합요법에 85.7% (6/7), cis-platin에 75.0% (9/12), bleomycin에 66.7% (4/6), cytoxan에 42.9% (3/7), 5-FU에 40.0% (4/10)의 양성반응을 보였다.
4. 신피막하 종양이식 분석법에 의한 화학감수성 검사결과와 임상적 치료효과를 비교한 바 전반적인 예상 정확도 (overall predictive accuracy)는 84.6%였다.

이상의 결과로 볼 때 신피막하 종양이식 분석법은 부인과 악성종양의 각종 항암제에 대한 화학감수성검사로서 임상적 치료효과의 예상 정확도가 높을뿐 아니라 시행하기가 용이하며 단시일내에 결과를 얻을 수 있기에, 임상에서 항암제 치료시 대단히 유용한 검사방법으로 사료된다.