Innovative therapy for refractory thyroid carcinomas

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Innovative therapy for refractory thyroid carcinomas

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ABSTRACT

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In general, thyroid carcinomas can be classified as well differentiated thyroid carcinomas and undifferentiated thyroid carcinomas. Fortunately, more than 95% of the thyroid carcinomas are well differentiated types showing favorable prognosis, and for these carcinomas, surgery with radioiodine ablation is the most effective therapy. However, only a few therapeutic options are available to treat the patients with undifferentiated thyroid carcinomas, especially with refractory thyroid carcinomas that are not amenable to surgery or radioiodine ablation. Recently, many institutions are under investigation to find a new treatment modality for such carcinomas. For the hope of finding an innovative drug therapy for refractory thyroid carcinomas, we investigated the anticancer effects of 20 drugs on 8 thyroid carcinoma cell lines. We analyzed the effects of 12 well acknowledged chemotherapy

drugs each tested at 3 different concentrations, and 8 additional chemotherapy and hormonal therapy drugs at 9 concentrations. In vitro chemosensitivity was tested using the adenosine-triphosphate-based chemotherapy response assay (ATP-CRA). The tumor inhibition rate (TIR; or cell death rate) or half maximal inhibitory concentration (IC_{50}) was analyzed to interpret the results. For 12 well acknowledged chemotherapy drugs, the active drugs showing better chemosensitivity were defined as those resulting in ≥30% TIR. Of the 12 chemotherapy drugs, etoposide and vincristine were the most active drugs showing the highest chemosensitivity and of the 8 additional drugs, trichostatin A showed favorable outcome as an anticancer drug. The study was to find an innovative therapy for the refractory thyroid carcinomas and the results showed that chemotherapy drugs such as etoposide and vincristine showed evidence as active anticancer drugs in thyroid carcinoma cell lines. Also, trichostatin A result came out to be the next promising drug. Further investigation of the above drugs and combination test for their interaction effects should be continued for clinical application in near future.

Key words: thyroid carcinoma cell lines, refractory thyroid carcinoma, chemotherapy drugs, hormonal therapy drugs, ATP-CRA

Innovative therapy for refractory thyroid carcinomas

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I. INTRODUCTION

In general, thyroid carcinomas can be classified as well differentiated thyroid carcinomas having favorable prognoses, and undifferentiated thyroid carcinomas having poor prognoses.[1,2] Fortunately, more than 95% of the thyroid carcinomas are well differentiated types, including papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), and their related variant types. However, the remaining 5% which includes anaplastic thyroid carcinoma (ATC), poorly differentiated types, and parafollicular C cell origin medullary thyroid carcinoma (MTC), show unfavorable disease processes despite an aggressive therapy.[3]

For thyroid carcinomas, surgery with thyroid stimulating hormone (TSH) suppression and radioiodine ablation (RIA) is the most effective therapy. In general, well differentiated

thyroid carcinomas such as PTC and FTC show excellent prognoses after the surgery with the combination of RIA according to the disease stage and many patients experience a curative or indolent clinical course.[4,5] Also, the prognosis after a local recurrence or distant metastasis for most of the well differentiated thyroid carcinomas are well controlled under the adequate re-operation or RIA.[5,6]

About 5% of the thyroid carcinoma is classified as undifferentiated type and although rare, ATC and MTC are usually resistant to the standard thyroid carcinoma treatment. At the time of diagnosis, ATC is usually unresectable, RIA resistant, and external radiation therapy has been used with no definite clinical survival benefits.[7,8] Postoperative RIA has no effect on MTC which is parafollicular C cell origin.[9,10]. Likewise, such lack of treatment modality is even worse especially with patients having refractory thyroid carcinomas. The refractory thyroid carcinomas are those not amenable to surgery, uncontrolled by RIA, iodine-refractory metastatic thyroid carcinomas, and carcinoma for which RIA is not an appropriate therapy.[11-13] To overcome these problems, many institutions are under investigation to find a new treatment modality for refractory thyroid carcinoma focused on the combination of drug chemotherapy, hormonal therapy and molecular targeted therapy.[11,14,15]

Previous studies about chemotherapy drugs for refractory thyroid carcinomas include doxorubicin, cisplatin, vincristine, cyclophosphamide, epirubicin and 5-fluorouracil.[9,16-20] Doxorubicin has been the most widely investigated drug analyzed for anticancer effect either by itself or in combination regimens.[21] However, such studies were performed only on few patients and yielded unsatisfactory results, with best of the results showing either limited

partial response or stable disease status.[10]

Due to these unsatisfactory outcomes, many studies about the etiology and oncogenic mutations of refractory thyroid carcinomas are underway, with the latter including mutations in the BRAF, RAS and RET/PTC genes.[22,23] In addition, drugs with different mechanisms have been developed mostly targeted at vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and tyrosine-kinase inhibitors.[21,24,25] To test these targeted drugs and to find an innovative drug therapy for refractory thyroid carcinomas, we have tested the effects of 20 drugs on 8 thyroid carcinoma cell lines.

II. MATERIALS AND METHODS

1. Cell lines

We cultured 8 thyroid carcinoma cell lines, 1 papillary (TPC-1), 4 follicular (WRO, FTC133, FTC236 and FTC238), 1 hürthle cell (XTC-1), 1 medullary (TT) and 1 anaplastic (FRO), all of which were purchased from American Type Culture Collection (Manassas, VA, USA) and all were originated from known tumors without laboratory cross-contamination.[26] TPC-1, FTC133, FTC236, FTC238, XTC-1, and TT cells were cultured by Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum (FBS), 100 U/mL penicillin, 100 μg/mL streptomycin and D-glucose. WRO and FRO cells were cultured by Roswell Park Memorial Institute (RPMI) medium supplemented with 10% FBS, 100 U/mL penicillin, 100 μg/mL streptomycin, 25 mM HEPES, and L-glutamine.

2. Chemotherapy and hormonal therapy drugs

The 12 well acknowledged chemotherapy drugs tested were 5-fluorouracil (5-FU), bleomycin, carboplatin, cisplatin, cyclophosphamide, doxorubicin, epirubicin, etoposide, methotrexate, oxaliplatin, paclitaxel, and vincristine. They were selected for their known anticancer effect and cytotoxicity for other malignancies, and that they have been previously studied on thyroid carcinomas. The 8 additional chemotherapy and hormonal therapy drugs tested were quercetin, resveratrol, rosiglitazone, sunitinib, tamoxifen, trichostatin A, valproic acid, and vandetanib. They were selected because their anticancer effect on other malignancies, especially breast carcinoma, has been reported but not clearly tested for thyroid carcinoma and some, not yet in clinical trial. The drugs were obtained from ISU ABXIS Co., Ltd. in Yonsei University Medical Center, Korea.

3. Evaluation of in vitro chemosensitivity

The cells were plated at 6000 cells per well in 96 well plates (Nunclon, Roskilde, Denmark) and cultured for 24 hours. Drugs were added to each well and incubated with the cells for 48 hours before the chemosensitivity test.

The assay used to test the chemosensitivity was adenosine-triphosphate-based chemotherapy response assay (ATP-CRA).[27] ATP is the basic energy source of all live cells and it is rapidly destroyed when cell death appear. The reduction in ATP luminescence is measured and compared with the untreated control cells. The increase in ATP reduction would mean better anti-cancer effect. By doing so, the tumor growth inhibition or cell death was compared between the drug treated cells and untreated control cells.

For the 12 well acknowledged chemotherapy drugs, we performed 3 test drug

concentrations (TDC)[27-29] at 20%, 100%, and 500% to calculate the chemosensitivity.[29] Tumor inhibition rate (TIR; or cell death rate) was calculated by measuring the reduction in ATP luminescence and compare with untreated control cell and the drug was defined as an active drug when TDC resulted in more than 30% TIR.[27] To calculate the TIR index value, the sum of TIR (20% ~ 500% TDC) was subtracted from 300, and this index value was used to rank the tested drugs which a lower value indicated a more active drug. The results of the 8 index values for each drug were averaged to calculate the mean index values. The cut-off mean TIR index value for determining more active drug was set at 100 for our study.

To evaluate the chemosensitivity of additional 8 drugs, we used the half maximal inhibitory concentration (IC_{50}).[30] The IC_{50} is a function antagonist assay which measures the effectiveness of a compound in inhibiting the biological or biochemical function. The IC_{50} of each drug was determined using the regression equation (Sigma Plot, California), $y=min + (max-min)/ (1+(x/EC50)^{Hill\ slope})$ and the lower value indicated a more active drug. Since the optimal drug doses for a recognizable activity against the thyroid carcinoma cell lines have not been clarified, the inhibition dependent dose ranges were obtained from nine different dose response curve, using cells treated with 1.875-300 μg/ml quercetin,[31,32] 0.39-800 μg/ml resveratrol,[33] 0.75-192 μg/ml rosiglitazone,[34] 0.0002-200 μg ml sunitinib,[35,36] 0.11-30 μg/ml tamoxifen,[37] 0.00469-1.2 μg/ml trichostatin A,[38] 777.6-2000 μg/ml valproic acid,[39,40] and 0.039-60 μg/ml vandetanib.[41,42] Recently, the studies about sunitinib and vandetanib are under active investigation by many other institutions.[43]

III. RESULTS

1. Well acknowledged chemotherapy drugs

Three TDCs (20%, 100%, and 500%) of 12 well acknowledged chemotherapy drugs were individually applied to 8 thyroid carcinoma cell lines (Table 1) to measure the TIR.

Table 1. The tumor inhibition rate of 12 well acknowledged chemotherapy drugs at 3 test drug concentrations.

	TDC* %	TPC-1	WRO	FTC 133	FTC 236	FTC 238	XTC-1	TT	FRO
5-FU**	20	41.5	43.0	44.8	32.0	50.2	15.5	0.0	60.5
	100	74.1	68.7	61.2	36.8	66.4	26.9	14.2	74.7
	500	77.6	77.9	75.7	54.1	79.1	50.9	43.7	89.2
bleomycin	20	17.4	0.0	60.0	9.8	22.1	44.2	20.5	24.8
	100	19.1	0.0	82.8	23.1	37.0	20.1	29.1	52.8
	500	30.3	0.0	93.4	35.8	64.0	4.4	38.1	85.9
carboplatin	20	2.5	0.0	8.2	4.8	12.7	9.7	14.6	7.7
	100	0.0	1.6	22.3	20.8	35.9	33.3	22.5	87.1
	500	32.1	52.1	92.4	84.5	92.8	75.2	51.3	78.3
cisplatin	20	7.8	0.2	12.2	9.1	17.6	23.5	0.0	8.1
	100	5.3	31.0	38.6	35.6	64.3	36.1	0.0	38.1
	500	70.5	67.3	91.0	81.5	93.7	70.7	30.3	93.8
CP†	20	7.6	0.0	2.1	9.0	9.3	0.0	0.0	10.3

	100	9.4	3.7	8.2	15.8	17.0	8.9	0.3	14.1
	500	29.8	22.0	69.0	41.4	80.2	99.3	81.1	94.8
doxorubicin	20	7.2	0.0	23.5	23.1	17.9	7.1	21.4	19.7
	100	46.1	15.7	51.1	62.8	52.8	10.5	36.2	49.4
	500	82.3	54.4	81.9	73.6	80.5	53.1	36.2	81.5
epirubicin	20	18.2	10.4	25.2	21.0	22.1	44.2	5.0	31.5
	100	39.0	24.9	47.0	62.1	59.1	29.4	24.1	60.4
	500	86.6	55.5	80.4	72.8	79.2	62.3	24.7	86.0
etoposide	20	21.2	0.5	69.9	74.1	61.6	38.7	20.4	65.8
	100	68.0	47.9	90.2	89.5	83.3	65.7	26.9	92.5
	500	97.8	72.7	95.3	89.8	89.2	74.1	97.8	88.7
MTX[††]	20	51.4	52.0	66.4	70.0	78.7	19.2	0.0	83.6
	100	59.0	54.9	75.6	75.7	82.0	23.2	7.4	86.8
	500	78.5	64.6	91.5	88.6	90.5	57.1	49.0	93.1
oxaliplatin	20	21.3	41.1	31.2	31.0	37.8	13.7	33.5	30.3
	100	25.2	62.6	40.4	43.6	43.3	20.6	80.5	38.0
	500	31.4	65.6	70.5	84.1	88.8	69.7	42.6	76.1
paclitaxel	20	98.3	52.9	80.5	64.9	75.7	0.0	0.1	86.8
	100	67.3	56.9	73.1	59.9	54.3	10.0	0.0	38.1
	500	87.5	84.7	89.1	75.9	59.1	0.0	83.0	93.9
vincristine	20	9.1	62.7	81.6	47.0	83.7	28.0	60.8	70.7
	100	93.8	61.7	83.9	49.1	83.9	29.8	82.6	70.5

500	95.3	61.2	86.9	50.8	85.2	30.5	88.0	71.6

*TDC; test drug concentration, **5-FU; 5-fluorouracil, †CP; cyclophosphamide, ††MTX; methotrexate

As shown in Figure 1, the mean TIR was calculated to analyze those drugs showing more than 30% TIR in cell lines. From 100% TDC results, we found that etoposide, vincristine and methotrexate, and 5-FU were the most active drugs, whereas cyclophosphamide the least active. Although drugs had a more than 30% TIR at 500% TDC, this concentration would be beyond clinical application. Even though all TIR did not increase in uniform pattern according to the TDC, we found that 5-FU, etoposide, methotrexate and vincristine showed a linear increase in TIR.

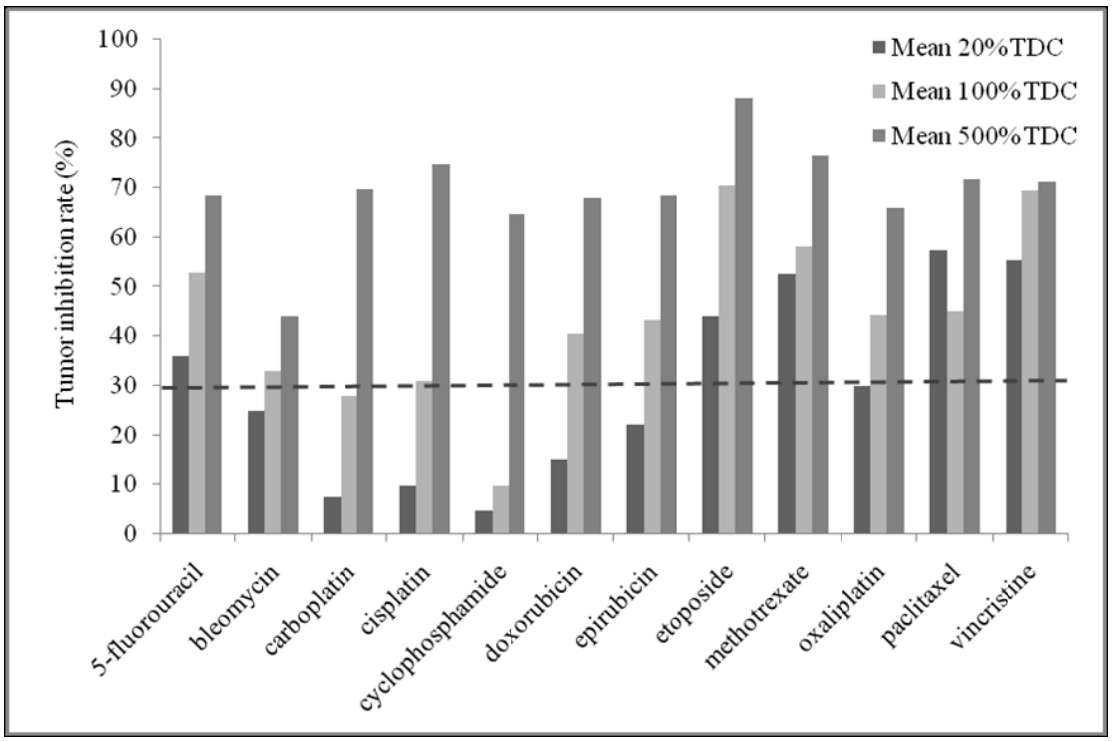


Figure 1. The mean of 8 thyroid carcinoma cell lines tumor inhibition rate (TIR) of 12 well acknowledged chemotherapy drugs at 3 test drug concentrations. The TIR value of 30% or more indicates that the drug is active and produces more desirable tumor inhibition outcomes. 5-FU, etoposide, methotrexate, and vincristine showed favorable results.

Then, we determined the TIR index value for each drug at 3 TDCs. In Figure 2, the mean TIR index values of 3 TDCs showed that vincristine and etoposide had the lowest values than the other drugs suggesting that these 2 drugs were more active in inhibiting thyroid carcinoma growth. In contrast, cyclophosphamide was observed as inactive.

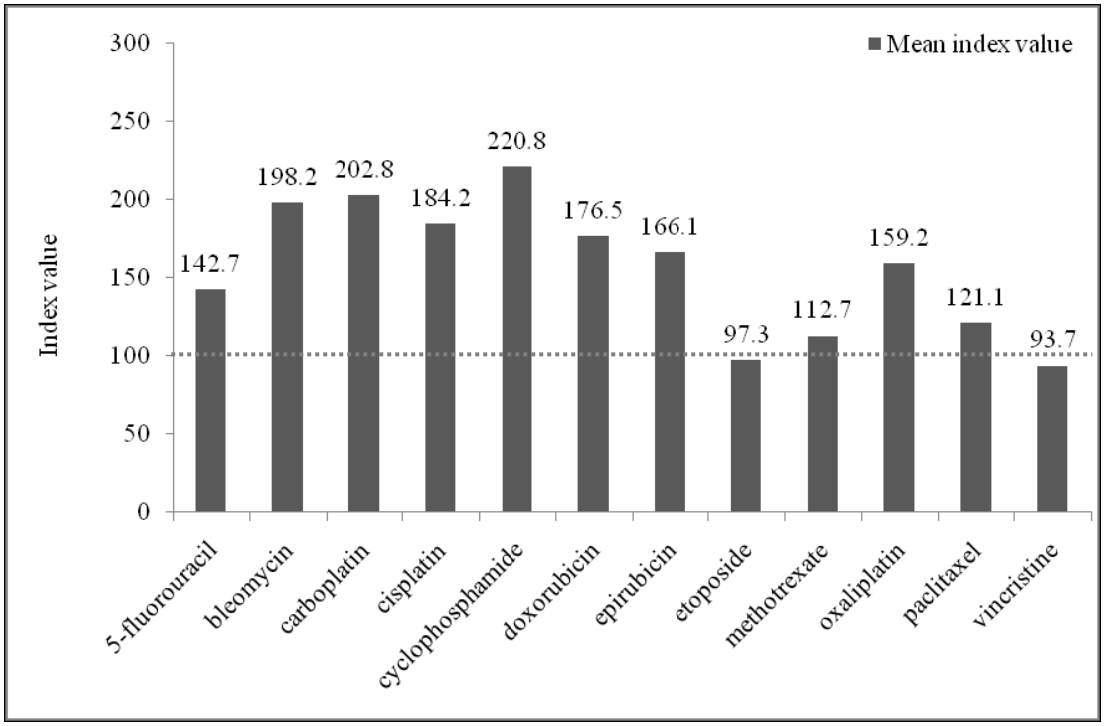


Figure 2. The mean TIR index values of 12 well acknowledged chemotherapy drugs. The

lowest mean index values were seen in etoposide and vincristine suggesting that these drugs are more active than others. The index value was calculated by subtracting the sum of tumor inhibition rate at 3 test drug concentrations from 300.

Next, we compared the mean TIR index values according to the types of thyroid carcinoma cell lines: papillary, follicular, hürthle cell, medullary and anaplastic (Figure 3). In this figure, paclitaxel and vincristine showed as most active drugs when cut-off mean index value set at 100. Etoposide, methotrexate, paclitaxel, and vincristine showed similar index values for follicular cell lines in general.

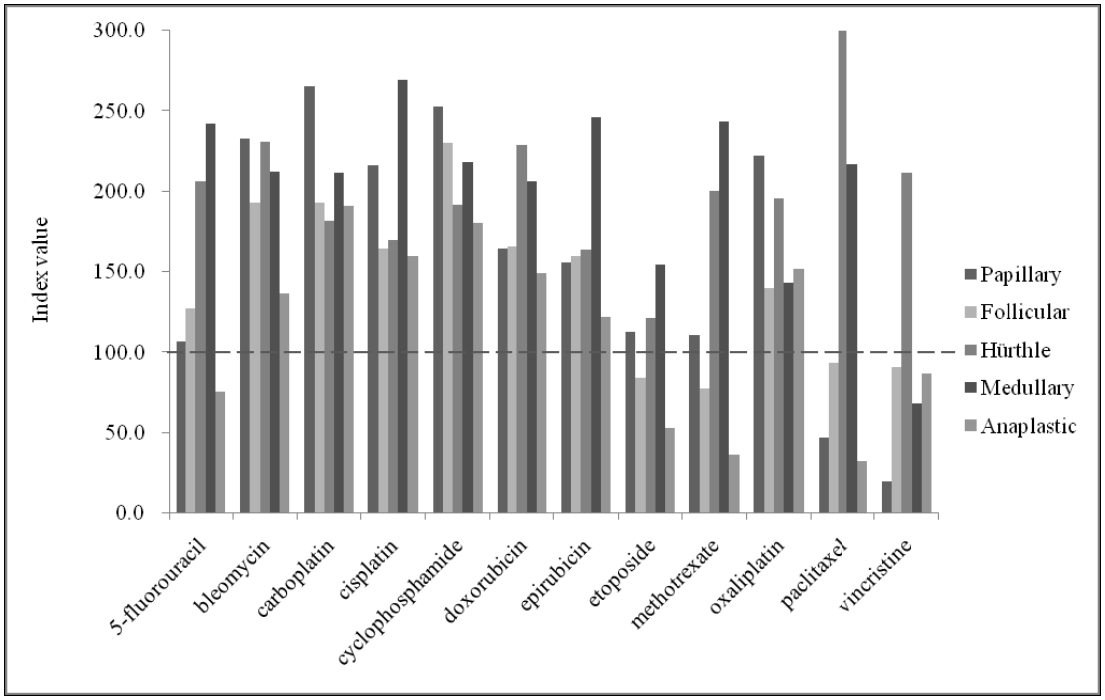


Figure 3. The mean TIR index values of 12 well acknowledged chemotherapy drugs applied

to 8 thyroid carcinoma cell lines analyzed according to the types of thyroid carcinoma cell lines. Papillary TPC-1, hürthle cell XTC-1, medullary TT and anaplastic FRO are single cell lines. Follicular cell lines are WRO, FTC133, FTC236 and FTC238 and the data shown are the mean value of 4 cell lines.

When these results were individualized by each cell lines, vincristine had the lowest index value of 19.8 in papillary TPC-1 cell. Also, paclitaxel showed favorable activity of 46.9. In follicular cell lines, etoposide and methotrexate showed potent activity in FTC133, FTC236, and FTC238. Vincristine was the only active drug in medullary TT cell and 5-FU, etoposide, methotrexate, paclitaxel, and vincristine showed activity in anaplastic FRO cell. Unfortunately, none of the tested drugs inhibited the growth of hürthle cell line, XTC-1 (Table 2).

Table 2. The TIR index values of 12 well acknowledged chemotherapy drugs at 3 concentrations applied to 8 thyroid carcinoma cell lines analyzed according to the types of thyroid carcinoma cell lines.

Index value*	TPC-1	WRO	FTC133	FTC236	FTC238	XTC-1	TT	FRO
5-fluorouracil	106.8	110.4	118.3	177.1	104.3	206.7	242.1	75.6
bleomycin	233.2	300.0	63.8	231.3	177.0	231.3	212.3	136.5
carboplatin	265.4	246.3	177.1	189.9	158.6	181.8	211.6	191.3
cisplatin	216.4	201.5	158.2	173.8	124.4	169.7	269.7	160.0

cyclophosphamide	253.2	274.3	220.7	233.8	193.5	191.8	218.6	180.8
doxorubicin	164.4	229.9	143.5	140.5	148.8	229.3	206.2	149.4
epirubicin	156.2	209.2	147.4	144.1	139.6	164.1	246.2	122.1
etoposide	113.0	178.9	44.6	46.6	65.9	121.5	154.9	53.0
methotrexate	111.1	128.5	66.5	65.7	48.8	200.5	243.6	36.5
oxaliplatin	222.1	130.7	157.9	141.3	130.1	196.0	143.4	151.8
paclitaxel	46.9	105.5	57.3	99.3	110.9	300.0	216.9	32.2
vincristine	19.8	114.4	47.6	153.1	47.2	211.7	68.6	87.2

*Index value: 300 – [sum of tumor inhibition rate at 3 test drug concentrations]

2. Additional chemotherapy and hormonal therapy drugs

We tested the chemosensitivity of the 8 additional chemotherapy and hormonal therapy drugs which were not well tested for thyroid carcinoma cell lines previously. The drugs were tested by determining their IC_{50} values to each cell line and we found that trichostatin A was the most active drug in all cell lines tested. The least active drug was valproic acid (Table 3).

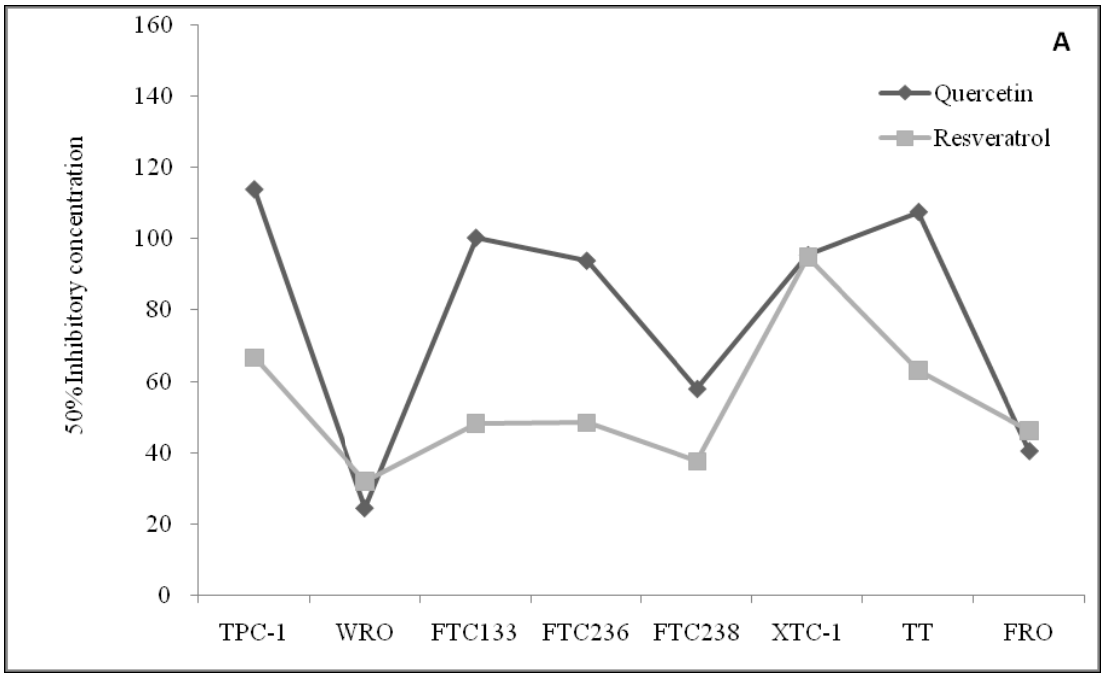
Table 3. The half maximal inhibitory concentration (IC_{50}) of 8 additional chemotherapy and hormonal therapy drugs.

IC_{50}*	Range (μg/ml)	TPC-1	WRO	FTC 133	FTC 236	FTC 238	XTC-1	TT	FRO
Quercetin	1.875	114.00	24.36	100.39	93.93	57.88	95.51	107.65	40.42

	~300								
Resveratrol	0.39 ~800	66.64	31.90	48.24	48.37	37.52	94.94	63.18	46.24
Rosiglita-zone	0.75 ~192	47.71	120.80	140.32	33.31	43.60	86.94	95.06	115.01
Sunitinib	0.0002 ~200	6.31	17.65	29.00	18.42	22.97	53.22	7.92	7.15
Tamoxifen	0.11 ~30	20.59	21.86	23.09	16.42	20.13	18.16	26.21	18.21
Trichosta-tin A	0.00469 ~1.2	0.06	0.03	0.05	0.06	0.07	0.05	0.05	0.05
Valproic acid	777.6 ~2000	1514.16	1936.43	1170.70	1451.52	1342.35	849.64	1419.75	776.16
Vandetanib	0.039 ~60	2.60	6.85	9.36	21.08	8.68	15.17	6.69	9.56

*IC_{50}; half maximal inhibitory concentration

To further understand the results of 4 drugs having similar cytotoxic mechanisms, we paired the results of quercetin and resveratrol; derived from grape-polyphenols, and sunitinib and vandetanib; small molecular tyrosine kinase inhibitors. Resveratrol and vandetanib showed lower IC_{50} values than quercetin and sunitinib, respectively (Figure 4).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Quercetin
Resveratrol
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TPC-1
WRO
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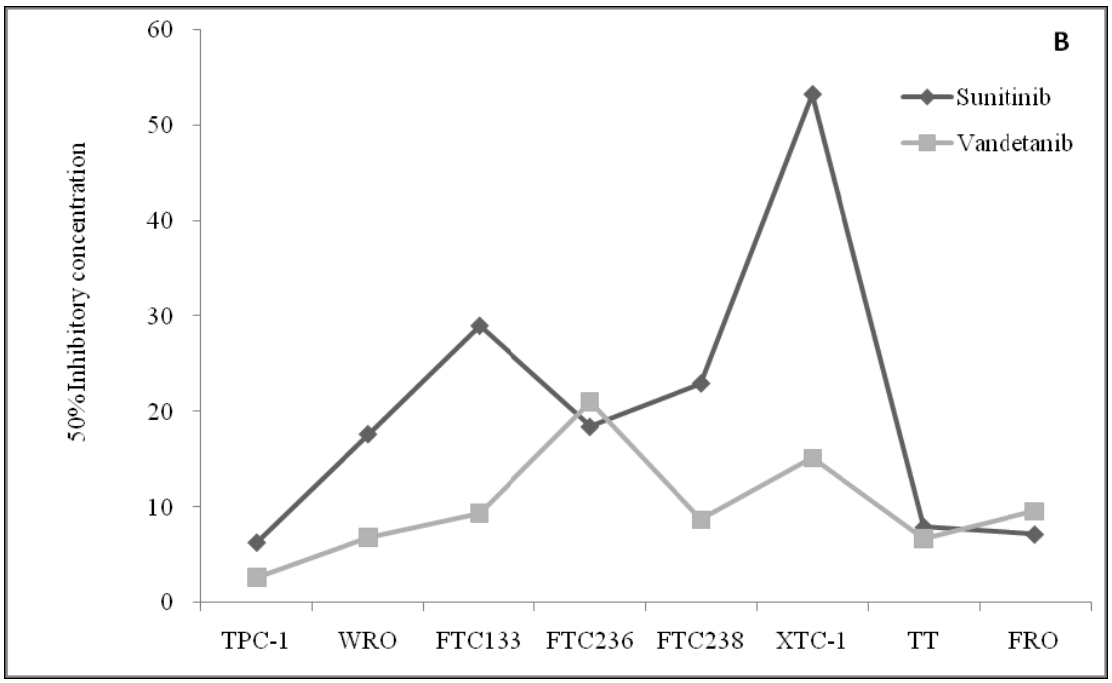
XTC-1
TT
FRO


B
Sunitinib
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50%Inhibitory concentration
60
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0
TPC-1
WRO
FTC133
FTC236
FTC238
XTC-1
TT
FRO

Figure 4. The half maximal inhibitory concentration (IC_{50}) of 4 additional drugs paired according to their similar cytotoxic mechanisms. Resveratrol showed lower IC_{50} than quercetin (A), and vandetanib than sunitinib (B) showing that resveratrol and vandetanib are more active drugs.

IV. DISCUSSION

Patients with intractable thyroid carcinoma typically have an unfavorable prognosis,[3] with refractory thyroid carcinoma having the most limited therapeutic options.[11-13] Recently, there have been studies of chemotherapy drugs to overcome such thyroid carcinomas.[14,15] We therefore tested 20 chemotherapy and hormonal therapy drugs in 8 thyroid carcinoma cell lines, all of which originated from refractory thyroid carcinomas. We found that 5-FU, etoposide, methotrexate, and vincristine showed favorable results in mean TIR each resulting in more than 30%. In addition, etoposide and vincristine had favorable mean index values for tumor growth inhibition. The previous studies focused on the combination chemotherapy indicated that doxorubicin, etoposide, paclitaxel, and vincristine were the most active drugs warranting further test.[8,9,17] In most of these studies, however, drugs were tested only against medullary or anaplastic thyroid carcinomas.[10] Fortunately, we yield a uniform result for etoposide and vincristine having favorable outcomes (Table 2).

Molecular targeted therapy and angiogenesis targeted therapies are also being investigated in patients with refractory thyroid carcinomas.[11,21,24] We found that trichostatin A had cytotoxic effect against refractory thyroid carcinoma cells. In other study, trichostatin A

has been shown to increase the effect of RIA in advanced thyroid carcinomas.[44] We also found that quercetin, resveratrol, sunitinib and vandetanib showed favorable results. Quercetin and resveratrol are grape-polyphenols that act as antioxidants, antiangiogenic agents and selective estrogen receptor modifiers. These drugs had beneficial effects in breast carcinomas and gynecologic diseases.[45] Sunitinib and vandetanib are multi targeted receptor tyrosine kinase inhibitors. These drugs, which block the VEGF receptors, thereby inhibiting tumor angiogenesis and proliferation, are currently being investigated in patients with refractory thyroid carcinomas.[21,46,47] Between the drugs having similar cytotoxic mechanisms, resveratrol and vandetanib were better than the counter drugs. In addition to these drugs, several other VEGF related drugs are being tested, including sorafenib (46), as well as tamoxifen, rosiglitazone and valproic acid.[39,48,49] Unfortunately, our study showed that cyclophosphamide and valproic acid were the least active drugs in tumor growth inhibition.

The limitation of this study is that the cell lines were cultured and tested without the prior information about gene mutation differences such as BRAF or RAS. Also, such drugs were tested in in vitro study and the results may differ in in vivo study. The toxicity control in in vivo study will be a challenge as well.

V. CONCLUSION

In our study, etoposide, vincristine, trichostatin A, resveratrol, and vandetanib showed prior favorable outcomes as the anticancer drugs in thyroid carcinoma cell line. These drugs may become an innovative therapy for refractory thyroid carcinomas in near future. Further

investigation of the above drugs and combination test of the active drugs for their interaction effect should be continued for clinical application. Also, selecting the patients to benefit from such therapy and deciding the primary end point as either overall survival of progression-free survival of such application would be another dilemma to solve.

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ABSTRACT (IN KOREAN)

난치성 갑상선암의 혁신적인 치료

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성 태 연

일반적으로 갑상선암은 분화 갑상선암과 미분화 갑상선암으로 구분하여 정의한다. 다행스럽게도 갑상선암의 95% 이상이 분화 갑상선암으로 이는 양호한 예후를 보이며 이런 경우, 수술과 방사성 요오드 제거술은 가장 효과적인 치료 방법이다. 하지만, 미분화 갑상선암에 있어서는 치료 방법이 매우 제한적이며 특히 난치성 갑상선암은 수술이나 방사성 요오드 제거술 치료에 반응하지 않는다. 따라서, 최근 많은 기관에서 이런 갑상선암의 새로운 치료 방법에 대해 연구 중이며, 본 논문은 난치성 갑상선암의 혁신적인 치료 방법을 찾기 위하여 8가지의 갑상선암 세포 주에 대해 20가지 항암 효과 약물을 적용하여 연구를 진행하였다. 현재까지 잘 알려진 12가지의 항암 약물은 각각 3개의 다른 약물

농도에서 그 효과를 분석하였으며, 8가지의 추가적 항암 약물과 호르몬 치료 약물은 9개의 농도에서 분석되었다. 체외 항암제민감성은 adenosine-triphosphate-based chemotherapy response assay (ATP-CRA) 를 이용하였으며 tumor inhibition rate (TIR; or cell death rate) 또는 half maximal inhibitory concentration (IC_{50}) 를 이용하여 결과값을 분석하였다. 12가지의 잘 알려진 항암 약물에서는 TIR 값이 30% 이상인 경우를 보다 나은 항암제민감성을 보이는 활동적인 약물로 정의하였으며 이 약물들 중에서 etoposide 와 vincristine 이 가장 활동적인 약물로 나타났다. 8가지의 추가적 항암 약물과 호르몬 치료 약물에서는 trichostatin A 가 가장 양호한 항암 효과를 기대 할 수 있는 약물이었다. 본 연구는 난치성 갑상선암 에서의 혁신적인 치료 방법을 찾고자 함 이였으며 연구 결과에서 etoposide 와 vincristine 이 활동적인 항암 약물로 나타났다. 또한, trichostatin A 가 앞으로 갑상선암에 대한 항암 효과를 기대해 볼 수 있는 약물로 나타났다. 위와 같은 약물들의 지속적인 연구와 더불어 이런 약물들 간의 상호 작용에 대한 결합성 연구는 향후 임상적 적용을 위해 계속 진행되어야 할 것이다.

핵심되는 말: 갑상선암 세포 주, 난치성 갑상선암, 항암 약물, 호르몬 치료 약물, ATP-CRA

PUBLICATION LIST

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