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Comparison of paclitaxel and docetaxel (Taxotere) in gynecologic and breast cancer cell lines with the ATP–cell viability assay

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The *in vitro* effects of paclitaxel (Tx) and docetaxel (Taxotere, Txt) are compared in this study using the adenosine triphosphate cell viability assay (ATP-CVA) in 14 cancer cell lines. Eleven cell lines were sensitive and three were partially sensitive to paclitaxel. Nine cell lines were sensitive, three were partially sensitive and two were resistant to docetaxel. Mean IC_{50}s were 3.7–660 ng/ml paclitaxel and 5.4–540 ng/ml docetaxel. In five sensitive cancer cell lines docetaxel was more active than paclitaxel, and in six sensitive cell lines paclitaxel was more active than docetaxel on a concentration basis. Two cell lines were sensitive to paclitaxel and resistant to docetaxel. In one cell line the two compounds had similar activities. In the ATP-CVA, paclitaxel and docetaxel are very active and are partially non-cross-resistant.

Key words: Anti-microtubule agents, ATP–cell viability assay, breast cancer, docetaxel, ovarian cancer, paclitaxel.

Introduction

Paclitaxel (Tx; NSC 125973) is a new anti-microtubule agent extracted from the bark of the Pacific yew *Taxus brevifolia*, with a unique mechanism of cytotoxic action.[1,2] In patients, Tx was found to be very active in ovarian and breast cancer.[3,4] In ovarian cancer about 30% partial and complete responses were reported.[3,4] In breast cancer patients, 56% objective remissions were reported.[5] The major concerns about Tx are its poor solubility and its limited availability. Efforts are undertaken to increase the supplies. One possibility would be semisynthetic production or the use of related compounds (taxoids). Docetaxel (Taxotere; Txt; RP 56976, NSC 628503) is such a compound. It is prepared from a precursor extracted from the needles of the yew *T. baccata*, providing a renewable supply for Txt preparation.[6] Preclinical studies with this drug showed very good activity in murine tumors and human tumor xenografts.[7–10] First experiences in phase I and II studies were made at different institutions in Europe and the United States. The drug has similar toxicities to Tx. Its anti-tumor activity is very promising, especially in breast, ovarian and non-small-cell lung cancers.[2,11] For comparison of *in vitro* toxicities in cancer cell lines between Tx and TXT, Ringel and Horwitz[12] used the incubation with different drug concentrations and cell counts after 72 h. Txt was two to five times more active than Tx, when comparing the abilities of the two drugs to promote tubulin polymerization.[13] Txt was significantly more active than Tx in nine human ovarian cancer cell lines in the sulforhodamine B assay.[14] In the colony-formation assay from different human tumors, Txt was more effective than Tx.[15] The disadvantages of *in vitro* screening with conventional assay systems and the application of the new ATP–cell viability assay (ATP-CVA; formerly ATP chemosensitivity assay or ATP-CSA) have been addressed elsewhere.[16,17] We used the ATP-CVA to test Tx in gynecologic cancer cell lines, breast cancer cell lines and gynecologic tumors.[18–20] The radiosensitizing effects of Tx were also studied using the assay.[21] The ATP-CVA is a very sensitive *in vitro* method for chemosensitivity evaluation.[12–24] The detection limit is 50 cells.[25] Preliminary correlations between *in vitro* chemosensitivity and *in vivo* response in gynecologic malignancies were promising.[16,17] We used this method to test standard drugs and their combinations, and to screen new drugs in cancer cell lines and human tumors.[16–21,26–30]

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Materials and methods

Cell lines

We analyzed Tx and Txt in 12 different gynecologic cancer cell lines and two breast cancer cell lines with the ATP-CVA. The cell lines used are listed in Table 1. AE 7 and ECC 1 were obtained from Dr B Satyaswaroop (Hershey, PA). These two cell lines were cultured from primary, untreated well-differentiated adenocarcinoma of the endometrium. BG 1 was obtained from J Johnson, Bowman Gray University. It was derived from an untreated patient. All other cell lines were purchased from American Type Culture Collection (Rockville, MD) and have a code identification number and a list of references. Table 1 summarizes in brief the characteristics, the patient provenence of the used cell lines and type of pretreatment. All cell lines were grown in Eagle's modified essential medium. The media contained 10% fetal bovine serum, 100 U/ml penicillin, 100 µg/ml streptomycin and 2.5 µg/ml amphotericin B. Cells were incubated at 37°C with 5% CO_2 and 95% humidity. Media were replaced every 3 days.

Table 1. Cell lines treated with paclitaxel and docetaxel

CA OV 3	From CAF-pretreated recurrent ovarian tumor
OVCAR 3	From CAP-pretreated recurrent ovarian tumor
SKOV 3	From CAT-pretreated recurrent ovarian tumor
BG 1	From untreated primary ovarian tumor
AE 7	From primary untreated well differentiated adenocarcinoma of endometrium
ECC 1	From primary untreated well differentiated adenocarcinoma of endometrium
HEC 1 A	From primary untreated moderately differentiated adenocarcinoma of endometrium
HEC 1B	From primary untreated moderately differentiated adenocarcinoma of endometrium
AN 3	From metastatic hormone-pretreated, poorly differentiated adenocarcinoma of endometrium
SKUT 1B	From radiation-pretreated, poorly differentiated uterine leiomyosarcoma
ME 180	From omental metastasis of a highly invasive radiation pretreated cervical cancer
SIHA	From metastatic cervical cancer
MCF 7	From invasive ductal breast cancer
T 47 D	From pleural effusion of a metastatic infiltrating ductal breast cancer

C,cyclophosphamide; A, adriamycin; P, cisplatin; F, 5-fluorouracil; T, thiotepa.

Table 2. Sensitivities to paclitaxel (Tx) and docetaxel (Txt)

Cell line	Sensitivity to Tx	Sensitivity to Txt
CA OV 3	sensitive	resistant
OVCAR 3	sensitive	sensitive
SKOV 3	partially sensitive	sensitive
BG 1	sensitive	sensitive
AE 7	sensitive	sensitive
ECC 1	sensitive	sensitive
HEC 1 A	partially sensitive	sensitive
HEC 1B	partially sensitive	resistant
AN 3	sensitive	sensitive
SKUT 1B	sensitive	partially sensitive
ME 180	sensitive	sensitive
SIHA	sensitive	sensitive
MCF 7	sensitive	partially sensitive
T 47 D	sensitive	partially sensitive

Sensitive: >70% ATP decrease; partially sensitive: 50–69% ATP decrease; resistant: <50% ATP decrease versus controls at 20% PPC.

Cells were subcultured weekly following detachment with 2.5 mg/ml trypsin per 0.02% EDTA.

Drugs

Tx was provided by the drug synthesis and chemistry branch, National Cancer Institute and from Bristol Myers (TAXOL). Txt was provided by Rhone Poulenc Rorer, France. We used a Tx peak plasma

Table 3. Comparison between the IC_{50}s of cisplatin, Tx and Txt in 14 cancer cell lines with the ATP-CVA

Cell line	Cisplatin (ng/ml)	Tx (ng/ml)	Txt (ng/ml)	Txt/Tx (%)
CA OV 3	1880	229	10.8	4.7
OVCAR 3	2430	72	128	180
SKOV 3	12500	45	162	360
AE 7	3950	215	17.6	8
ECC 1	3721	11.5	5.4	47
HEC 1 A	12500	570	54	9
HEC 1B	8475	660	270	41
AN 3	1350	10.4	50.5	500
SKUT 1B	2100	242	282.6	116
ME 180	1750	252	48.6	20
SIHA	2125	109.5	108	100
MCF 7	925	41.4	540	1300
T 47 D	700	3.68	162	4400
Mean	4039	209	134	506
SD	4062	215	147	1173

$P < 0.002$ (Tx *vs* cisplatin); $p < 0.4$ (Tx *vs* Txt)
IC 50, Drug concentration producing 50% decrease of cellular ATP *vs* controls; PPC, peak plasma concentration (2.5 µ/ml cisplatin; 5 µM = 4270 ng/ml Tx and 4040 ng/ml Txt).

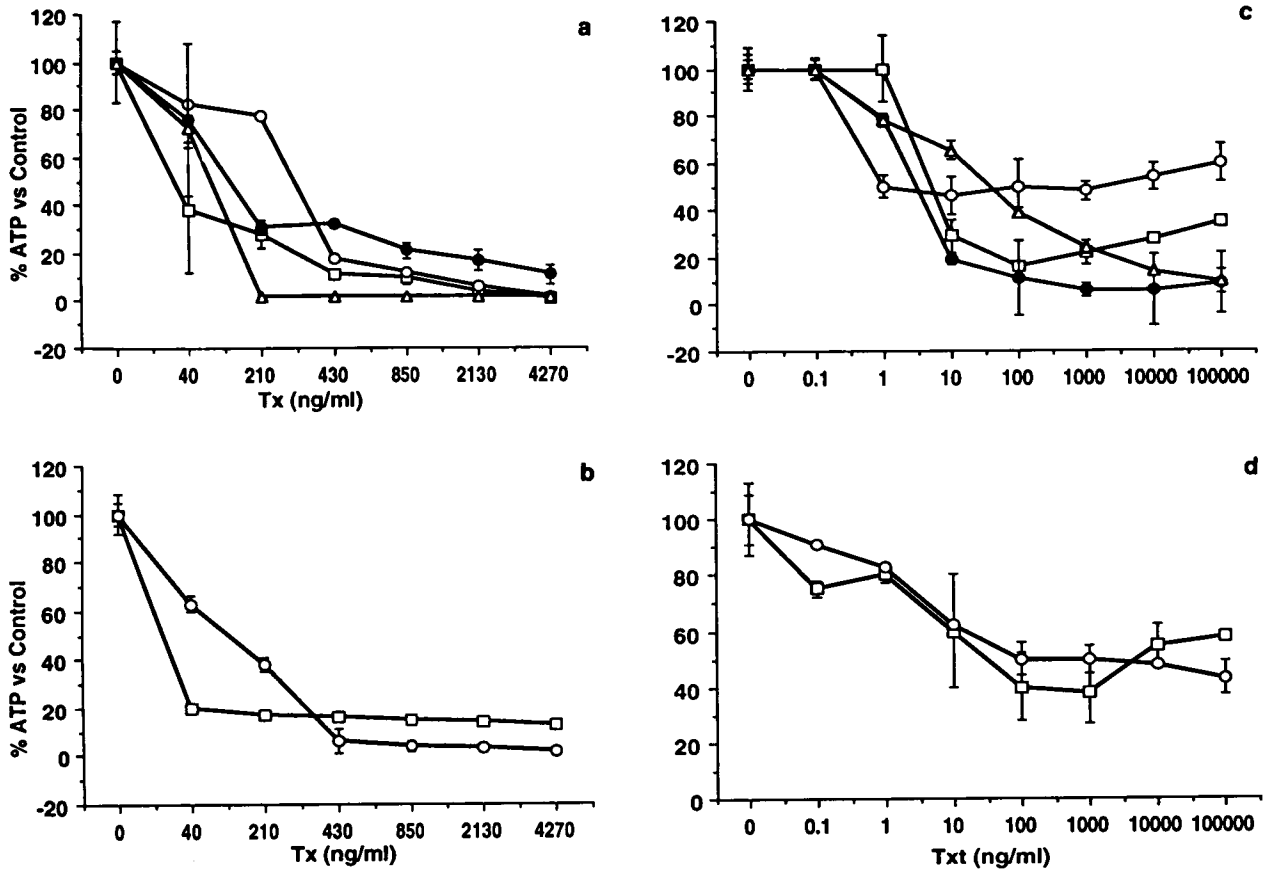

Figure 1. Dose related ATP decrease after treatment with different doses of paclitaxel (Tx) (a,c) and docetaxel (Txt) (b,d) in four ovarian cancer cell lines (a,b): BG 1 (□); CAOV 3 (○); SKOV 3 (●); OVCAR 3 (△), and two breast cancer cell lines (c,d): T 47 D (□) and MCF 7 (○).

concentration (PPC) of 5 μM = 4270 ng/ml, corresponding to the average area under the curve obtained from pharmacokinetic studies in patients with a range of 1–10 μM.[31] The PPC of Txt was not available from patient studies when we started our *in vitro* experiments. Therefore we used seven different dilutions, to allow comparison with Tx on a concentration basis. We used 4040 ng/ml Txt as PPC. At the maximum tolerated dose, 100 mg/m^2 over 1 h, which is the recommended duration for phase II, the PPC of Txt from a recent publication is 3800 ng/ml.[2] Our range in the ATP-CVA covers a wide area below and above this concentration. Tx and Txt were received as sterile lyophilized powder. A stock solution of 10 mg/ml was made in dimethylsulfoxide (DMSO), the further dilutions were made in Hawk's balanced saline solution prior to each assay. The final maximal concentration of DMSO in the tumor cell containing wells was 0.02%.

ATP-CVA

Suspensions of 20 000 cells/ml were plated in 24-well plates in triplicates. The following Tx concentrations were used: 0, 40, 210, 430, 850, 2130 and 4270 ng/ml. The Txt concentrations were: 0, 0.1, 1, 10, 100, 1000, 10 000 and 100 000 ng/ml. Drug exposure was performed for 90 min 24 h after plating. Untreated controls were measured on days 0, 3 and 6 in triplicates. ATP was extracted with 4% trichloroacetic acid *in situ*. A 0.2 ml aliquot was removed from the well and neutralized with 0.4 ml 0.1 M Tris buffer, pH 9.0, resulting in a final pH of 7.3. Luminometric analysis was performed using the luciferin–luciferase reaction (Los Alamos Diagnostics, NM). This complex produces measurable light in the presence of ATP. The ATP concentration correlates strongly with the *in vitro* cell count.[16,25] The average amount of luminescence from triplicate

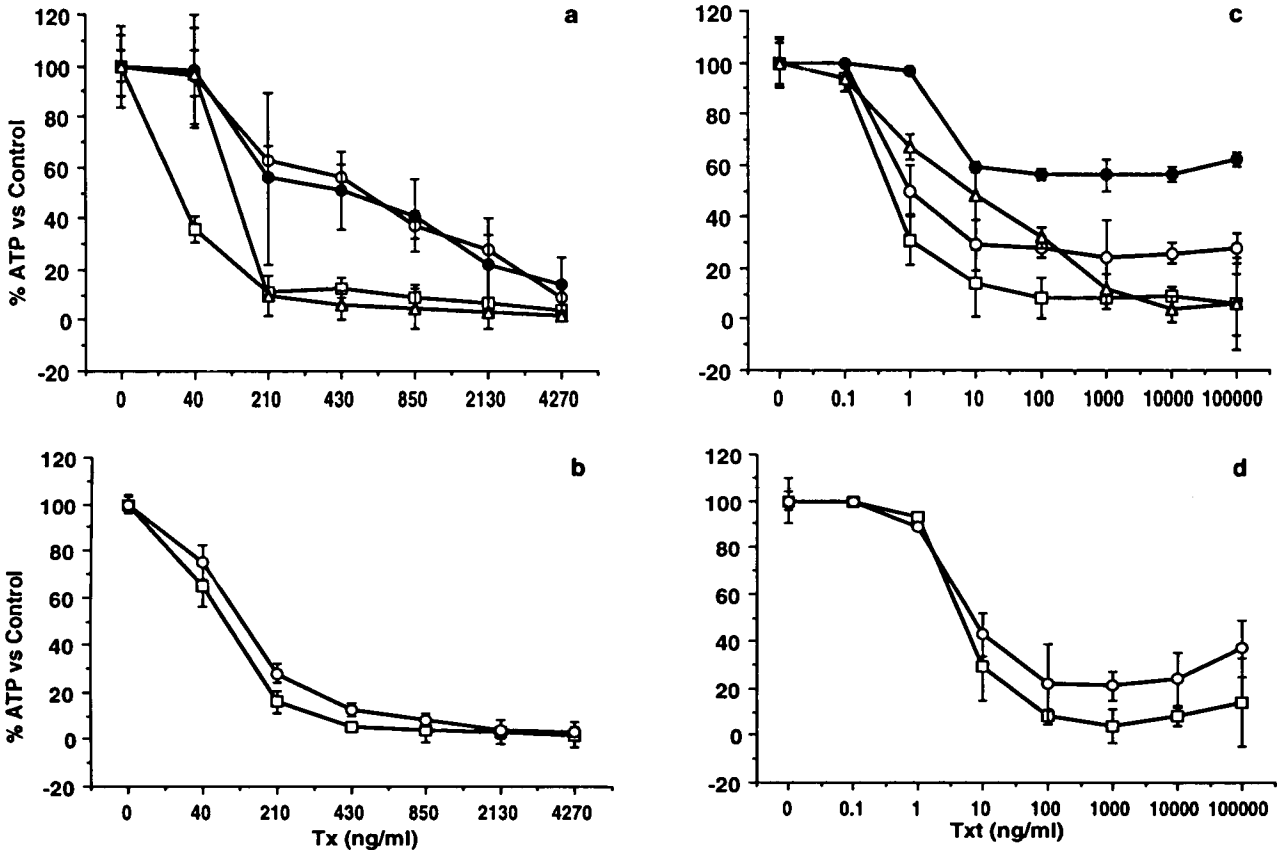

Figure 2. Dose-related ATP decrease after treatment with different doses of paclitaxel (Tx) (a,c) and docetaxel (Txt) (b,d) in four endometrial cancer cell lines (a,b): ECC 1 (□); HEC 1A (○); HEC 1B (●); AE 7 (△), and two cervical cancer cell lines (c,d): ME 180 (□) and SIHA (○).

samples was compared between controls and drug-treated wells in order to quantify the cytotoxic effects of the different drugs.

Data analysis

Average ATP concentrations and coefficient of variation were calculated for controls and each drug concentration. Sensitivity (S) was defined as 70% or more reduction; partial sensitivity (PS), 50–69% and resistance (R), 0–49% ATP reduction, compared with controls at 20% of the PPC. IC_{50} (the drug concentration needed to produce ≥50% decrease of cellular ATP) was calculated from median effect analysis plotting log (F_a/F_u) *vs* log C (F_u = fraction unaffected or surviving fraction, F_a = fraction affected = 1 − F_u, C = concentration[32]). From repeated experiments, coefficients of variation varied from 2 to 18%.

Results

Table 1 lists all cell lines evaluated with the ATP-CVA. In Table 2 sensitivities of these cell lines to Tx and Txt are shown. All cell lines except the ovarian cancer cell line SKOV 3 and the endometrial cancer cell lines HEC 1A and HEC 1B were sensitive to Tx according to the ATP-CVA definition of sensitivity. These three cell lines were partially sensitive to Tx. The highly cisplatin-resistant cell line BG1[29] was Tx and Txt sensitive. The ovarian cancer cell line CAOV 3 and the endometrial cancer cell line HEC 1B were Txt resistant. Both tested breast cancer cell lines were partially sensitive to Txt. Table 3 shows all IC_{50}s for cisplatin, Tx and Txt in the 14 cancer cell lines and compares the differences between Txt and Tx. The breast cancer cell line T 47 D showed the lowest IC_{50} of 3.7 ng/ml Tx. The highest IC_{50} was found in the endometrial cancer cell line HEC 1B, with 660 ng/ml Tx. The IC_{50}s in the cisplatin resis-

tant ovarian cancer cell line BG1 were 45 ng/ml for Tx and 162 ng/ml for Txt (the IC_{50} of cisplatin from former studies with the ATP-CVA in our laboratory was >12 500 ng/ml).[29] The mean values of the two drugs are not statistically different (Student's *t*-test) for all cell lines. In individual cell lines there are marked differences. The differences between the IC_{50}s of Txt and Tx are shown in Table 3. They varied between 9 and 4400%. From former studies in our laboratory with the ATP-CVA in cancer cell lines, IC_{50}s of cisplatin were also calculated.[20,21,29,30] These values are shown in Table 3. As noted, mean IC_{50} values of cisplatin varied between the different cell lines. The most important finding was, that on a concentration basis Tx and Txt were several times more active than cisplatin in the tested cancer cell lines.

Figure 1 demonstrates the differences between cytotoxicities of Tx and Txt in four ovarian and two breast cancer cell lines. Figure 2 summarizes these results in four endometrial and two cervical cancer cell lines. Figure 3 shows the results in the metastatic and sarcoma cell line AN3 and SKUT, respectively. In Figure 4, IC_{50}s of all tested cancer cell lines are shown. In the four ovarian cancer cell lines, dose–response curves were similar with Tx. After Txt treatment, the major cytotoxic effects occurred between 1 and 100 ng/ml. Further dose increase had no significant additional effects. In the two breast cancer cell lines a very similar pattern of response was noted. In the cancer cell lines AN 3 and SKUT the major cytotoxic effects occurred between 40 and 210 ng/ml Tx, and between 1 and 1000 ng/ml Txt. The endometrial cancer cell line

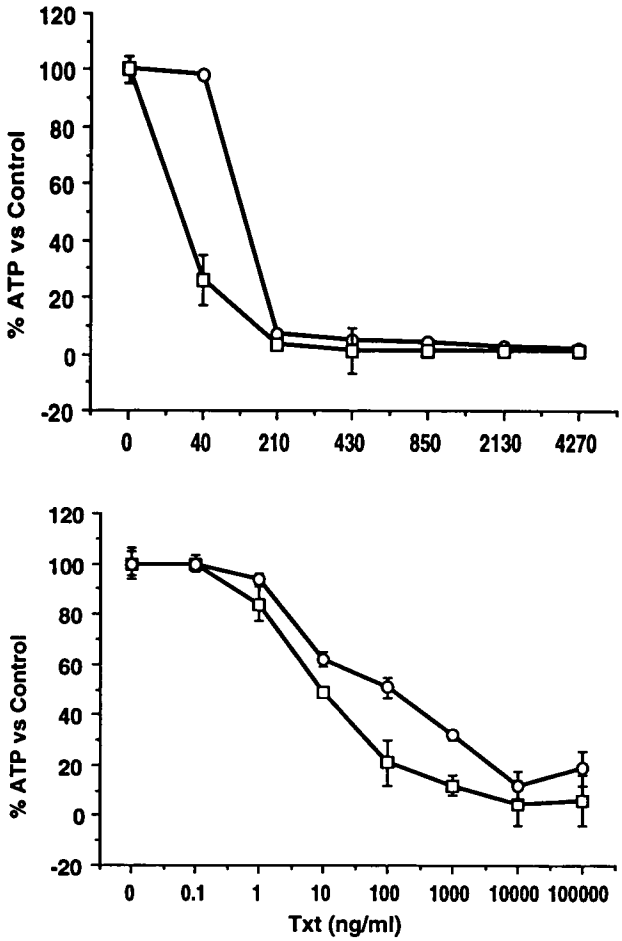

Figure 3. Dose-related ATP decrease after treatment with different doses of paclitaxel (Tx) (top) and docetaxel (Txt) (bottom) in two cancer cell lines: AN 3 (□; metastatic endometrial adenocarcinoma) and SKUT 1 B (○; uterine leiomyosarcoma).

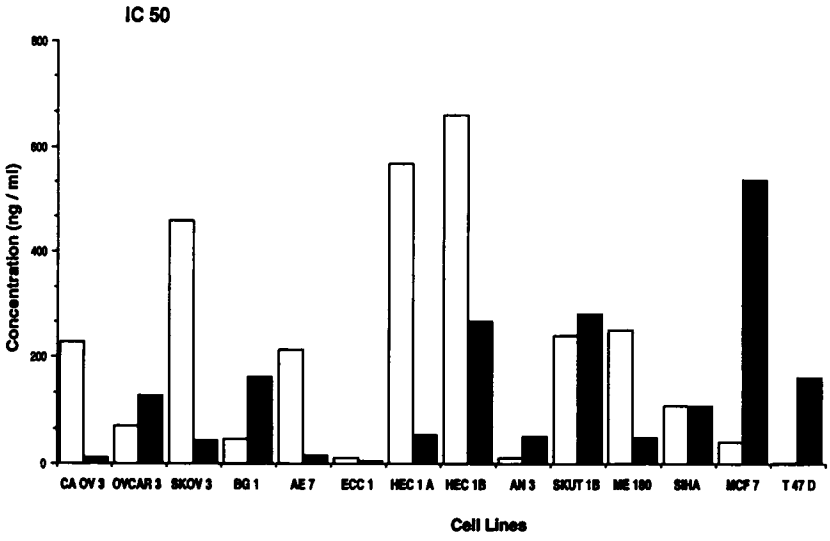

Figure 4. IC_{50}s of 14 gynecologic and breast cancer cell lines calculated from ATP-CVA dose–response curves after treatment with paclitaxel (□) or docetaxel (▨).

ECC 1 already showed cytotoxic effects at 40 ng/ml Tx and 1 ng/ml Txt. Two of the endometrial cancer cell lines (HEC 1A and HEC 1B) needed doses of Tx higher than 850 ng/ml to show a significant ATP decrease. A similar pattern was seen in HEC 1A with Txt. In HEC 1B, no additional effects were seen after a dose increase above 10 ng/ml Txt, even at the highest concentrations. ECC1 and AE 7 showed an almost linear dose–effect relationship between 0.1 and 1000 ng/ml Txt. The cervical cancer cell lines ME 180 and SIHA showed similar effects after treatment with Tx and Txt. Maximum cytotoxic effects were reached with 430 ng/ml Tx and 100 ng/ml Txt.

Discussion

We used 12 different gynecologic cancer cell lines and two breast cancer cell lines to detect differences between the activities of Tx and Txt with the ATP-CVA. This was an approach to the *in vivo* situation, where tumor heterogeneity is a challenging therapeutic problem. There are several reports about preclinical differences of these two drugs.[14,15] On a concentration basis, Txt is often found to be more active than Tx.[12–15] Our observation of incomplete crossresistance has been reported by others, and is of special interest.[14,15,33,34] In our study, the activities of the two drugs with the ATP-CVA are heterogenous. Some of the tested cancer cell lines exhibited partially non-cross-resistance to Tx and Txt. The responsible mechanism for this finding is not known. Some reports assume this to multi-drug resistance (*mdr*) gene expression.[34] The *in vitro* differences in activity compared with cisplatin previously reported[14] could also be demonstrated with our assay. This may have therapeutic consequences. The transposition of *in vitro* data to the *in vivo* situation may cause some problems. Nevertheless, the ATP-CVA is a reliable short-time assay, can be performed easily and seems to predict correctly synergism between cisplatin and Tx in ovarian cancer specimens.[19] A preliminary report with this combination in suboptimally debulked ovarian cancer demonstrated possible advantages compared with standard combinations.[35] In view of our *in vitro* results, Tx and Txt should be seen not as competitive drugs, but as challenging new anti-cancer agents, which may have a different spectrum of activity within a given disease and open a completely new area of investigation in oncology.

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