Mitoxantrone Combined with Paclitaxel as Salvage Therapy for Platinum-refractory Ovarian Cancer: Laboratory Study and Clinical Pilot Trial

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ABSTRACT

This report describes preclinical and early clinical investigations of the mitoxantrone/paclitaxel combination (NT) for patients with platinum-refractory ovarian cancer. The preclinical activity of NT was studied ex vivo, evaluating native tumor specimens with the ATP tumor chemosensitiv-

INTRODUCTION

Primary ovarian carcinomas frequently respond to chemotherapy. Remission rates of 60–70% have been observed after platinum-based first-line therapy, reducing the relative risk of progression and death to 0.7 (1, 2). Nevertheless, the majority of patients with advanced disease will relapse, resulting in an overall 5-year survival of only 20% (1, 2). The likelihood of relapsing patients to respond to either second-line platinum or nonplatinum regimens strongly depends on the disease-free interval after completion of initial chemotherapy (2–6). The probability that platinum-refractory patients (i.e., those presenting with primary progression or recurrence after ≤6 months) will benefit from salvage chemotherapy is limited (2, 3, 6, 7). Paclitaxel (Taxol®), ifosfamide, and altretamine are considered to be the most active single agents in this setting, but at conventional dosages, they produce RR4 of no more than 30% (2, 6, 7). Unfortunately, higher RRs achieved with dose-escalated paclitaxel do not translate into improved PFS and OAS, respectively (6, 8, 9). Introduction of paclitaxel into first-line therapy of ovarian cancer (10) may even create more problems with recurrent disease. Recently, altretamine and topotecan have been considered the most effective agents in this setting (11, 12), whereas modest activity was demonstrated for gemcitabine and reintroduction with either carboplatin or paclitaxel (13–15). Therefore, the search for new salvage regimens remains an important goal to improve treatment for patients with platinum-refractory ovarian cancer.

Paclitaxel exhibits synergistic cytotoxicity with a number of other agents. In a pilot trial of NT was initiated for patients with platinum-refractory ovarian cancer. All seven patients achieved complete remission (NT-I, three; NT-II, four) with a median progression-free survival of 40 weeks. During 92 NT courses, myelosuppression with leucopenia, anemia, and thrombocytopenia was the limiting toxicity, occurring more frequently with NT-II. No patient required hospitalization due to any life-threatening complication. Five complete and nine partial remissions were observed with both NT-I and NT-II, accounting for an overall 78% response rate, with a median progression-free survival of 40 weeks. One patient showed early progression during therapy. Currently, three patients (NT-I, two; NT-II, one) have died due to progressive relapsed ovarian cancer, so that the median overall survival is not reached after a median follow-up of 40.5+ weeks. Both schedules were found to be equal in terms of response rate and overall survival. NT is highly active and practical for salvage treatment of ovarian cancer. NT-II may be preferred due to both clinical activity and patients’ acceptance. However, NT-I seems to be a less myelotoxic alternative. Both schedules warrant further clinical investigation.

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4 The abbreviations used are: RR, response rate; ATP-TCA, ATP tumor chemosensitivity assay; CR, complete response; G-CSF, granulocyte colony-stimulating factor; MI, maximum inhibition; NC, no change; NT, mitoxantrone/paclitaxel; OAS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SI, sensitivity index; TDC, test drug concentration.
of cytostatics, including platinum and doxorubicin, for a variety of animal and human tumors (16). Previous preclinical studies performed in our laboratories used the ATP-TCA (17) to investigate the activity of the doxorubicin/paclitaxel combination in native ovarian carcinomas (18). This method is a valuable approach for ex vivo testing of clinical tumors and provides major advantages over classical chemosensitivity assays in terms of efficacy, reproducibility, robustness, and evaluability (17, 19). Clinical correlations are promising for both ovarian (17, 20) and breast tumors (19). Based on these investigations, we observed well-tolerated activity of doxorubicin/paclitaxel in patients with platinum-refractory ovarian cancer who had failed both single agents (21). The clinical utility of this combination, however, may be compromised by the considerable nonhematological side effects of doxorubicin. In particular, cardiotoxicity and mucotoxicity of doxorubicin can be potentiated when used in combination with paclitaxel (22-24).

The synthetic anthracenedione mitoxantrone (Novantrone) can often be regarded as a clinical substitute for anthracyclines (23, 25). It compares favorably to doxorubicin in terms of its markedly reduced organ toxicity (25, 26). In tests of perioperative breast and ovarian carcinomas, our laboratories have previously demonstrated that both agents usually have similar activity, but there seem to be instances of non-cross-resistance in which mitoxantrone may be superior to doxorubicin (27, 28). In a variety of human cancer cell lines and some perioperative tumors, we and others have found NT to be highly synergistic and, therefore, possibly the best combination (28, 29).

Doxorubicin/paclitaxel is at the forefront of clinical investigation for breast cancer (30) and exhibits preclinical and clinical activity against recurrent ovarian cancer as well (21, 31). NT represents a logical next step that may be less toxic. This article describes new evidence that NT has high preclinical activity against tumor cells taken directly from patients with platinum-refractory ovarian carcinoma. Based on these ex vivo results, we have initiated a pilot study of NT at two different schedules in heavily pretreated ovarian cancer patients. All had previously failed platinum-based chemotherapy. This report summarizes the first results of this clinical trial.

MATERIALS AND METHODS

Preclinical Studies

Tumor Samples. The preclinical evaluation of NT used tumor samples taken directly from 24 patients with platinum-refractory recurrent ovarian cancer, 17 solid tumors and 7 malignant ascitic fluids. Tumor material was sampled under sterile conditions and immediately transferred to the laboratory. Surgical specimens were transported in HBSS (Life Technologies, Inc., Paisley, United Kingdom) supplemented with 300 units/ml penicillin and 300 μg/ml streptomycin. Malignant effusions were stored natively after adding preservative-free sodium heparin (Vetren 200; Promonta, Hamburg, Germany) at 25-50 units/ml.

Chemosensitivity Testing. Chemosensitivity was assessed using the ATP-TCA. This assay uses commercially available test kits (TCA-100; DCS Innovative Diagnostik Systeme, Hamburg, Germany) that include all required material not otherwise identified. ATP-TCA methodology has been described in detail (17, 19, 27).

Briefly, tumor cells were isolated by mechanical and enzymatic dissociation and subsequent Ficoll gradient centrifugation (Lymphoprep; ICN Flow, Muckenheim, Germany). Viability and quality of cell suspensions were determined by trypan blue dye exclusion (0.2%; Merck, Darmstadt, Germany) and cytological examination, respectively. Approximately 10,000–20,000 cells were then seeded into each well of a 96-well polypropylene microwell. Commercial formulations of mitoxantrone (Novantron; Cyanamid-Lederle, Wolfratshausen, Germany) and paclitaxel (Taxol®, Bristol-Myers Squibb, Munich, Germany) were used for this investigation. Single agents and the combination were tested at six different TDCs (i.e., 6.25–200% TDC) with 0.6 μg/ml mitoxantrone and 13.6 μg/ml paclitaxel as 100% TDC (14, 24). Each TDC was tested in triplicate. Additionally, both no inhibition (M0) and MI controls were set up for each microwell.

Assay Evaluation. After 5–7 days of culture at 37°C in a humidified 5% CO2, 95% air atmosphere, ATP was extracted from the cells and subsequently measured luminometrically using the luciferin-luciferase firefly reaction. Comparing treated cells with both controls, individual tumor growth inhibition (TGI) was calculated as:

\[ \text{TGI} = \left[ 1 - \frac{(\text{TDC} - \text{MI})}{(\text{M0} - \text{MI})} \right] \times 100 \]  

(1)

Individual dose-response curves were constructed for both drugs and the combination, respectively. IC50 and IC90 were determined by linear interpolation. Four categories of ex vivo sensitivity were defined as (27): (a) strong sensitivity, IC90 ≤100% TDC and IC50 ≤25% TDC; (b) partial sensitivity, IC90 >100% TDC and IC50 ≤25% TDC; (c) weak sensitivity, IC90 ≤100% TDC and IC50 >25% TDC; and (d) resistance, IC90 >100% TDC and IC50 >25% TDC.

Ex vivo RR was defined as:

\[ \text{RR}_{\text{ex vivo}} = \frac{(\text{all tumors tested} - \text{resistant tumors})}{(\text{all tumors tested})} \]  

(2)

Additionally, a SI represented by the area under the inhibition curve was calculated by trapezoidal transformation, with high values indicating high sensitivity, and low values evidencing resistance ex vivo (17, 27). Drug interactions were analyzed by the sigmoid model described by Pöschl (32). Assuming that both single agents act independently on tumor cells, a theoretical dose-response curve for the combination was constructed for each tumor. Drug interactions were defined as independent if the experimental dose-response curve was equal to the theoretical one. Potentiation was assumed if NT produced a significantly higher cell kill, as could be expected theoretically. In tumors showing an experimental dose-response curve inferior to the theoretical one, drug interactions were regarded as relative antagonism (if NT was superior to the best single agent) or absolute antagonism (if the best single agent was superior to NT).

Clinical Trial

Patients. Since November 1994, 15 patients with histologically confirmed platinum-refractory ovarian carcinoma...
on days 1 and 2 followed by a 24-h infusion of 180 mg/m² of both chest and abdomen, if indicated. or CA 19-9), transvaginal and abdominal ultrasound, thoracic X-ray scans, and computed or magnetic resonance tomography staging including serum marker measurements (CA 125, CEA, recovery from surgery.

The regimen was thus modified in the remainder to provide an optimized protocol for future Phase II/III trials. This schedule used a 6 mg/m² bolus injection of mitoxantrone on day 1 followed by a 1-h infusion of 100 mg/m² paclitaxel on days 1 and 8 (NT-II). The whole course was repeated on day 15. Between courses 3 and 4, treatment was interrupted for 1 week. G-CSF was used if leukocytes were <2,000/µl or the neutrophils were <1,000/µl. Delayed hematological recovery in spite of G-CSF or any severe organ toxicity required both dose reduction or interval prolongation until recovery of bone marrow or any other involved organ. In responding patients, a maximum of six NT courses was administered. Therapy was discontinued in patients with evidence of either progression or unresolved life-threatening toxicities.

**Evaluation of Toxicity.** Patients enrolled in this trial were regarded as eligible for toxicity if they received at least one course of NT. All adverse effects were monitored and recorded using the WHO score. Toxicity was assessable for all 18 NT therapies.

**Evaluation of Response.** Therapy was monitored by measurements of the appropriate serum marker preceding each NT course. Tumor evaluation was performed every 6 weeks by transvaginal ultrasound, X-ray scan or computed tomography of the chest, and computed or magnetic resonance tomography of the abdomen, respectively. Additional tumor imaging was performed at any time when progression was suspected. A minimum of two NT cycles was required to classify a patient as evaluable for response. Responses were assessed using standard criteria: (a) CR, complete disappearance of all measurable tumor and normalization of elevated serum markers for a minimum of 4 weeks; (b) PR, a ≥50% decrease in the sum of the products of two diameters of all measurable lesions or (clinical CR with elevated tumor markers) for at least 4 weeks; (c) NC, any condition distinct from CR, PR, or PD; and (d) PD, a ≥25% increase in the sum of two diameters of all measurable lesions or the appearance of new metastases.

**Follow-Up.** All patients entered a follow-up program including gynecological checks, transvaginal ultrasound, and measurements of tumor markers every 3 months. Tumor imaging was performed as appropriate. OAS and PFS were measured from the start of the first NT course. All causes of death were used to calculate OAS. PFS was defined as the minimal interval between commencing NT therapy and evidence of progression, death, or loss to follow-up.

**Statistics.** Statistical calculations were performed using GraphPAD software (San Diego, CA). SI values for mitoxantrone, paclitaxel, and NT were analyzed by repeated measure ANOVA. Differences in ex vivo RR were analyzed by extended χ² tests. Survival analyses were performed using Kaplan-Meier procedures. For all statistical calculations, \( P \leq 0.05 \) indicated significance.

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**Table 1** Patterns of chemosensitivity ex vivo exhibited by 24 perioperative ovarian cancer specimens

<table>
<thead>
<tr>
<th>Drug(s) tested</th>
<th>Sensitivity</th>
<th>Partial sensitivity</th>
<th>Weak sensitivity</th>
<th>Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitoxantrone</td>
<td>3</td>
<td>–</td>
<td>4</td>
<td>17</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>NT</td>
<td>13</td>
<td>–</td>
<td>7</td>
<td>4</td>
</tr>
</tbody>
</table>

" Response rate ex vivo: mitoxantrone, 7 of 24 (29%); paclitaxel, 8 of 24 (33%); NT, 20 of 24 (83%).

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Fig. 1. Distribution of SIs for mitoxantrone (○), paclitaxel (□), and the combination NT (△) in 24 platinum-refractory ovarian cancers tested ex vivo with the ATP-TCA. Horizontal lines, mean values.
1530 NT in Refractory Ovarian Cancer

RESULTS

Preclinical Studies

All 24 drug assays were evaluable. Mean SI values for all three regimens are presented in Fig. 1. NT was significantly more active compared to both mitoxantrone ($P < 0.01$) and paclitaxel ($P < 0.001$). Patterns of preclinical chemosensitivity are summarized in Table 1. *Ex vivo* RRs for mitoxantrone (29%) and paclitaxel (33%) did not differ significantly, whereas NT produced a significantly higher RR of 83% ($P < 0.0001$). Strong sensitivity was observed in 13 of 20 tumors responding to NT. Seven tumors resistant to both single agents exhibited sensitivity to the combination. In 10 tumors, drug interactions showed potentiation according to the $P$ch model (32). In an additional nine samples, both agents were found to act independently. In only five tumors, relative or absolute antagonism was obvious.

Clinical Trial

Toxicity. A total of 92 NT courses were administered (NT-I, 56 courses; NT-II, 36 courses); all were evaluable for toxicity. The predominant adverse effect was myelosuppression with grade 3-4 leukopenia, grade 3 thrombocytopenia, and grade 3-4 anemia occurring during 59, 7 and 9% of cycles. Myelotoxicity was seen more frequently in patients receiving NT-II, with 75% of cycles complicated by grade 3-4 leukopenia. In comparison, grade 3-4 leukopenia was observed during 48% of NT-I cycles. Severe thrombocytopenia and anemia were seen in 4 and 7% of NT-I cycles and in 11 and 11% of NT-II cycles, respectively. However, bone marrow function recovered spontaneously in most cases within 3-5 days or was successfully supported by G-CSF required during 10 of 18 treatments (56%). There were no febrile episodes seen with NT at either schedule.

In patient P. U., the last two NT-II cycles were administered with 4 mg/m² mitoxantrone and 70 mg/m² paclitaxel due to both persistent grade 3 thrombocytopenia and grade 4 anemia requiring erythrocyte transfusion. In patients P. F. and M. E., NT-I treatment was delayed for 7-11 days due to leukopenia in spite of G-CSF support. As expected, all patients experienced grade 2-3 alopecia. With the exception of grade 3 nausea/vomiting occurring during one cycle of NT-I and grade 3 malaise/fatigue observed during five courses of NT-II, nonhematological side effects such as peripheral neuropathy, myalgia, diarrhea, or mucositis were generally mild (grade 1-2) and occurred infrequently. There were no symptomatic bradycardia or other cardiotoxic complications, nor did any patient require hospitalization due to infection or other life-threatening events.

Clinical Activity. All patients treated with NT received at least two courses, and all were evaluable for response. The median follow-up is 40.5+ weeks. Table 2 summarizes patients’ characteristics and their therapeutic outcome. Objective responses were seen in 14 patients (5 CR and 9 PR), resulting in an overall 78% RR. Remissions were achieved with both NT schedules and tended to be long enough to have clinical utility. Median OAS is not yet reached, and median PFS is 40 weeks (Fig. 2). Although CRs were achieved with NT-I only, RR for NT-II was slightly higher, but not significantly so (NT-I, 73%; NT-II, 86%). Patient K. G., who experienced a PR of 50-week duration after treatment with NT-I and grade 3 malaise/fatigue observed during five courses of NT-II, nonhematological side effects such as peripheral neuropathy, myalgia, diarrhea, or mucositis were generally mild (grade 1-2) and occurred infrequently. There were no symptomatic bradycardia or other cardiac complications, nor did any patient require hospitalization due to infection or other life-threatening events.

Table 2 Patients’ characteristics and therapeutic outcome

<table>
<thead>
<tr>
<th>Patient (initials)</th>
<th>Age (yrs)</th>
<th>Prior chemotherapy*</th>
<th>Metastatic site*</th>
<th>NT schedule†</th>
<th>No. of NT courses</th>
<th>Quality of response</th>
<th>TPP‡ (wks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. B.</td>
<td>43</td>
<td>aCP, EPI, aCC</td>
<td>Pelvis, abdomen</td>
<td>I</td>
<td>6</td>
<td>CR</td>
<td>88+</td>
</tr>
<tr>
<td>M. C.</td>
<td>48</td>
<td>CC, CP</td>
<td>Pelvis, abdomen</td>
<td>I</td>
<td>6</td>
<td>CR</td>
<td>76+</td>
</tr>
<tr>
<td>M. E.</td>
<td>55</td>
<td>CP, VP-16</td>
<td>Pelvic, paraaortic LNS</td>
<td>I</td>
<td>3</td>
<td>NC</td>
<td>65+</td>
</tr>
<tr>
<td>B. F.</td>
<td>67</td>
<td>CP</td>
<td>Pelvis, abdomen, lung</td>
<td>I</td>
<td>2</td>
<td>PD ~ (alive)</td>
<td></td>
</tr>
<tr>
<td>P. F.</td>
<td>63</td>
<td>CC</td>
<td>Abdomen, abdominal wall, subhepatic LNS</td>
<td>I</td>
<td>6</td>
<td>NC</td>
<td>55 (dead)</td>
</tr>
<tr>
<td>K. G. (a)</td>
<td>45</td>
<td>CP</td>
<td>Pelvis, subhepatic LNS</td>
<td>I</td>
<td>6</td>
<td>PR</td>
<td>50 (alive)</td>
</tr>
<tr>
<td>K. G. (b)</td>
<td>46</td>
<td>CP, NT-I</td>
<td>Pelvis, liver, spleen capsule</td>
<td>II</td>
<td>6</td>
<td>PR</td>
<td>28</td>
</tr>
<tr>
<td>K. G. (c)</td>
<td>46</td>
<td>CP, NT-I, NT-II</td>
<td>Pelvis, spleen</td>
<td>II</td>
<td>6</td>
<td>PR</td>
<td>16</td>
</tr>
<tr>
<td>E. K.</td>
<td>63</td>
<td>CC</td>
<td>Pelvis, abdomen</td>
<td>II</td>
<td>4</td>
<td>NC</td>
<td>10+</td>
</tr>
<tr>
<td>M. J. (a)</td>
<td>67</td>
<td>CC, PTX</td>
<td>Subhepatic and paraaortic LNS</td>
<td>II</td>
<td>4</td>
<td>PR</td>
<td>28</td>
</tr>
<tr>
<td>M. J. (b)</td>
<td>68</td>
<td>CC, PTX, NT</td>
<td>Subhepatic, retroperitoneal, sigma</td>
<td>II</td>
<td>6</td>
<td>PR</td>
<td>20+</td>
</tr>
<tr>
<td>R. R.</td>
<td>64</td>
<td>CC, PTX, CP</td>
<td>Subhepatic and paraaortic LNS</td>
<td>II</td>
<td>6</td>
<td>PR</td>
<td>15+</td>
</tr>
<tr>
<td>B. R.</td>
<td>35</td>
<td>CC, CI, ICE (high dose)</td>
<td>Pelvis, pelvic and paraaortic LNS, bursa omentalis</td>
<td>I</td>
<td>6</td>
<td>CR</td>
<td>40 (alive)</td>
</tr>
<tr>
<td>U. R.</td>
<td>55</td>
<td>CP, TEO</td>
<td>Pelvis, abdomen, paraaortic LNS</td>
<td>I</td>
<td>2</td>
<td>PR</td>
<td>36+</td>
</tr>
<tr>
<td>T. S.</td>
<td>49</td>
<td>CC</td>
<td>Pelvis, abdomen</td>
<td>I</td>
<td>6</td>
<td>CR</td>
<td>20+</td>
</tr>
<tr>
<td>M. S.</td>
<td>55</td>
<td>CP</td>
<td>Pelvis, paraaortic LNS</td>
<td>I</td>
<td>6</td>
<td>CR</td>
<td>23 (dead)</td>
</tr>
<tr>
<td>R. T.</td>
<td>58</td>
<td>CP, CC, VP-16, PI</td>
<td>Pelvis, pelvic LNS</td>
<td>I</td>
<td>6</td>
<td>PR</td>
<td>20+</td>
</tr>
<tr>
<td>P. U.</td>
<td>40</td>
<td>CC, aCP, CPA, AT</td>
<td>Pelvis, hepatic and paraaortic LNS, spleen</td>
<td>II</td>
<td>4</td>
<td>PR</td>
<td>22 (dead)</td>
</tr>
</tbody>
</table>

* The abbreviations used are: aCC, cytosine arabinoside/carboplatin; aCP, cytosine arabinoside/cisplatin; AT, doxorubicin-paclitaxel; CC, cyclophosphamide/carboplatin; CI, cyclophosphamide/cisplatin; CP, cyclophosphamide/cisplatin; CPA, cyclophosphamide; EPI, epirubicin; ICE, ifosfamide/carboplatin/etoposide; PI, cisplatin/ifosfamide; PTX, paclitaxel; TEO, treosulfan; VP-16, etoposide.

*b LNS, lymph nodes.

† I, NT-I; II, NT-II.

‡ TPP, time to progression. +, patients still on response.
was discontinued after two cycles. Three patients (NT-I, two patients; NT-II, one patient) have died due to progressive recurrent tumor at 32, 37, and 62 weeks from the start of NT. The remainder are still alive, and nine are even progression-free (NT-I, six patients; NT-II, three patients).

**DISCUSSION**

Taxanes such as paclitaxel are considered the most active agents in platinum-refractory recurrent ovarian cancer, producing a 25-30% RR and a median PFS of 6 months (2, 6-8, 22, 36). Increasing the paclitaxel dose may increase the RR, but this, unfortunately, did not improve survival (8, 9, 37).

In various preclinical studies, paclitaxel was shown to act synergistically with a number of standard cytostatics, including topoisomerase II inhibitors (16). In a clinical trial based on prior *ex vivo* evaluation of fresh tumor specimens (18), we found doxorubicin/paclitaxel to have well-tolerated activity in ovarian cancer patients who had failed both platinum and single-agent paclitaxel (21). Testing a limited number of human tumor cell lines, Glück *et al.* (29) observed a strong synergism between paclitaxel and mitoxantrone that compared favorably with other paclitaxel-based combinations including doxorubicin, etoposide, cyclophosphamide, or platinum (29). Mitoxantrone is less cardiotoxic and mucotoxic than doxorubicin, and lack of cross-resistance has been demonstrated for various clinical tumors in a considerable number of patients (25, 26, 38, 39). Both the promising clinical activity of doxorubicin/paclitaxel and the confirmed preclinical experiences provide evidence that NT should be regarded as a logical next step in developing a well-tolerated regimen for the treatment of platinum-refractory recurrent ovarian carcinoma.

The ATP-TCA may be useful for *ex vivo* chemosensitivity testing of clinical tumors and seems to be applicable to anthracyclines and taxanes (18, 27, 28). It possibly provides major advantages over classical chemosensitivity assays in terms of efficacy, reproducibility, robustness, and evaluability, with promising clinical correlations reported for both ovarian and breast cancers (17, 19, 20). This assay was thus considered a suitable model to assess the preclinical activity of NT in native platinum-refractory ovarian cancers.

Generally, the *ex vivo* results described herein show activity for both mitoxantrone and paclitaxel that is consistent with clinical experience (8, 36, 40). The combination produced an unexpectedly high rate of antineoplastic activity *ex vivo*. Seven tumors with apparent resistance to both single agents were sensitive to NT. *Ex vivo* resistance is a highly reliable predictor of clinical resistance (41); thus, reversal of resistance as we found here is a noteworthy success. The analysis of the effect of the NT combination indicates potentiation or at least major independent activity for both drugs in the majority of tumors. Although the reasons for these effects are not clear at present, our findings argue in favor of a real synergism between the drugs.

Our first clinical results provide evidence that NT given at either schedule has acceptable toxicity and produces exceptionally high clinical efficacy in patients with platinum-refractory ovarian cancer. Compared to clinical results with doxorubicin/paclitaxel described by us and others (21, 31), NT seems to be a further improvement. Both the 78% RR and particularly the response duration observed in this study compare favorably with those achieved with other salvage therapies such as paclitaxel, docetaxel, altretamine, ifosfamide, or topotecan (2, 6-8, 11, 12, 22, 36, 42). These findings therefore challenge the traditional view that drug combinations have no advantage for salvage therapy of ovarian carcinoma as compared to single agents (42). Work in progress seeks the optimal dosage for NT-II, which may be preferred for future evaluation because this regimen combines both high clinical activity and convenience for the patients. However, NT-I seems to be a reasonable alternative to NT-II, particularly in patients with impaired bone marrow function or in those who are otherwise unable to undergo weekly chemotherapy.

Responses in ovarian cancer patients failing both platinum and paclitaxel are rare. In this setting, altretamine and topotecan are the only drugs with proven major clinical activity (11, 12). Therefore, the activity of NT that we have found in patients pretreated with paclitaxel alone or in combination is of particular interest. Considering the published single-agent activities of mitoxantrone (35) and paclitaxel (8, 22, 36), the results of this pilot trial provide evidence for a clinical synergism between these drugs that parallels our previous and current laboratory experience (28). We made similar observations with platinum
and cytosine arabinoside even when both single agents were completely inactive (43, 44). Moreover, it should be noted that NT clearly produced a higher clinical activity than doxorubicin/paclitaxel, although this was not expected from the preclinical and clinical single-agent activities (18, 21, 23, 25, 31). Modern ex vivo test systems such as the ATP-TCA thus provide an effective and time-saving method for the preclinical selection of innovative chemotherapy regimens for further clinical use. In conclusion, NT showed unusually promising anticancer activity in heavily pretreated patients with platinum-refractory ovarian cancer, without producing nontolerated toxicity. This combination should thus be considered for large-scale clinical trials.

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