Taurolidine: Cytotoxic and Mechanistic Evaluation of a Novel Antineoplastic Agent

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ABSTRACT

Bis-(1,1-dioxoperhydro-1,2,4-thiadiazinyl-4)methane (taurolidine) is a synthetic broad-spectrum antibiotic that reacts with bacterial cell membrane components to prevent adhesion to epithelial cell surfaces. Reflecting the key role of adhesion in the growth and development of human solid tumors, studies were initiated to assess the antiproliferative activity of this agent in selected human and murine tumor cell lines. A 3-day exposure to taurolidine inhibited the growth of all of the cell lines evaluated with IC_{50} ranging from 9.6–34.2 \mu M. Studies to identify the mechanism responsible for this effect were conducted in NIH-3T3 murine fibroblasts and the PA-1 and SKOV-3 human ovarian tumor cells. These studies revealed that a 48-h exposure to taurolidine had little effect on cell cycle distribution in PA-1 and SKOV-3 cells but significantly increased the appearance of DNA debris in the sub-G_0/G_1 region, an effect consistent with an induction of apoptosis. In contrast, in NIH-3T3 cells, taurolidine exposure did not increase DNA debris in the sub-G_0/G_1 region. Additional studies assessed phosphotidylserine externalization after a 24-h exposure to taurolidine using annexin-V binding as a cell surface marker. These studies revealed that taurolidine increased the percentage of annexin-V-positive cells by 4-fold and 3-fold in PA-1 and SKOV-3 cells, respectively. In NIH-3T3 cells, taurolidine exposure slightly increased (–5%) annexin-V binding. Parallel studies revealed that exposure to taurolidine also resulted in poly(ADP-ribose) polymerase cleavage in both ovarian tumor cell lines but not in NIH-3T3 cells. Finally, murine-based studies were conducted to assess the antineoplastic activity of three consecutive daily i.p. bolus injections of taurolidine at doses ranging from 5-mg injection/mouse to 30-mg injection/mouse. The 20-mg injection dose produced –10% mortality and was identified as the maximally tolerated dose in this model. Administration of this regimen to nude mice bearing i.p. human ovarian tumor xenografts significantly inhibited both tumor formation and growth. These findings are discussed in light of their clinical implications.

INTRODUCTION

The antibiotic taurolidine^3 was synthesized in the 1970s by Geistlich-Pharma, Inc. (Ref. 1; Fig. 1). Early studies (2–7) revealed that it possessed bactericidal activity against a broad spectrum of aerobic and anaerobic bacterial strains as well as clinically relevant fungi. In contrast to other antibiotics, the activity of taurolidine depends upon a chemical reaction secondary to the generation of active methyol groups formed upon the decomposition of the parent molecule (Refs. 2, 8, 9; Fig. 1). Biochemical and morphological studies (7, 10, 11) revealed that these methylol-containing moieties appeared to react with bacterial cell wall components to prevent the adherence of microorganisms to biological surfaces such as epithelial cells. In addition to this direct effect on bacterial cell wall components, taurolidine has been reported to reduce tumor necrosis factor \alpha synthesis and activity (12–15). Finally, the ability of taurolidine to affect cell surface structure and function apparently is responsible for its observed ability to reduce the extent and severity of postoperative peritoneal adhesions. Reflecting these multiple activities, taurolidine has been administered clinically, by lavage, after abdominal surgery to reduce postoperative infections and adhesions and to treat peritonitis (2, 16–19).

Advanced ovarian carcinoma is an important cause of cancer-related deaths in the United States, and it is estimated that in the year 2000 approximately 14,000 women died of this disease (20). Upon initial presentation, ovarian cancer is often in an advanced stage and metastatic to the peritoneal cavity. Many patients with advanced ovarian cancer initially respond to surgery and chemotherapy. However, these responses are usually short-lived, and the majority of these patients will have disease recurrent to the peritoneal cavity. There is no effective treatment for recurrent metastatic ovarian cancer (21–23).

Accordingly, we initiated studies to assess the potential antineoplastic activity of taurolidine in human ovarian carcinoma and a variety of other human tumor cell lines. We now report that this agent inhibited the growth of all of the tested human tumor cell lines in vitro, and mechanistic studies revealed that this effect correlated with the induction of apoptosis in tumor cells. Furthermore, antineoplastic evaluation of taurolidine in nude mice bearing i.p. xenografts of human ovarian tumors demonstrated that this agent significantly inhibited tumor development and growth. Preliminary aspects of these studies have been reported (24, 25), and the clinical implication of these findings are discussed.

MATERIALS AND METHODS

Reagents. Taurolidine was generously provided by Carter-Wallace, Inc. (Cranbury, NJ) as a 2% solution in 5% Kollidon 17PF. Cell culture growth media (high glucose DMEM, RPMI 1640, McCoy’s 5A, and F12K), trypsin, and fetal bovine serum were purchased from Life Technologies, Inc. (Grand Island, NY). Disposable cell culture supplies were obtained from Fisher Scientific (Medford, MA). The annexin-V/FTTC assay kit was purchased from Clontech (Palo Alto, CA). Reagents for SDS-PAGE were purchased from Bio-Rad Laboratories (Richmond, CA). A murine monoclonal antibody (clone C-2-10) to human PARP was purchased from Zymed Laboratories (San Francisco, CA). All of the other chemicals were purchased from Sigma Chemical Co. (St. Louis, MO).

Cell Lines. Cell growth inhibition assays were conducted in a panel of human solid tumor cell lines and in NIH-3T3 murine fibroblasts. Tumors represented in this panel were ovarian (PA-1 and SKOV-3), colon (HCT-8, HCT-15, and HT-29), lung (H-157, A-549, and H-596), prostate (DU-145), glioblastoma (U-251), and melanoma (MNT-1). These lines were obtained from the American Type Culture Collection. Also included in the cell panel was the murine melanoma B16F10, which was a gift from Dr. Vincent J. Hearing (NIH, Bethesda, MD). Cells were maintained in appropriate growth medium at 37°C in a humidified incubator in an atmosphere of 5% CO_2. The doubling time of all of the cell lines was 20–28 h.

Animals. Antineoplastic activity was determined in 6–12-week-old female homozygous athymic (Hsd:athymic nude nu/nu) mice obtained from Harlan (Indianapolis, IN).

Cell Growth Inhibition Assays. Subconfluent cell cultures were harvested by trypsinization and resuspended in media at a cell density of 1–5 \times 10^4 \text{ cells/mL}. One ml of this suspension was added to each well of a 12-well cell culture plate that contained 3 ml of media plus serum. Twenty-four h later, taurolidine was added in a volume of 40 \mu l to achieve a final concentration of 0.1–200 \mu M. Control wells received 40 \mu l of 5% Kollidon 17PF alone.
The taurolidine doses evaluated were 5, 10, 15, 20, 25, and 30 mg/mouse per single i.p. bolus injection on 3 consecutive days, was initiated. To evaluate therapeutic effectiveness (31–33), mice received a single i.p. injection of 5 × 10⁶ SKOV-3 cells in 0.5 ml. Immediately thereafter, mice were randomly divided into treatment groups of seven animals. Taurolidine therapy, consisting of a single i.p. bolus injection of 20 mg of taurolidine on 3 consecutive days, was initiated at selected time intervals thereafter (≤5 days). Control animals received 1-ml injections of 5% Kollidon 17PF alone. Animals were examined daily, and body weight was recorded twice weekly. A reduction in body weight of greater than 10% was considered significant. The maximally tolerated dose was chosen as the dose that produced ~10% mortality (31–33).

To evaluate therapeutic effectiveness (31–33), mice received a single i.p. injection of 5 × 10⁶ SKOV-3 cells in 0.5 ml. Immediately thereafter, mice were randomly divided into treatment groups of seven animals. Taurolidine therapy, consisting of a single i.p. bolus injection of 20 mg of taurolidine on 3 consecutive days, was initiated at selected time intervals thereafter (≤5 days). Control animals received 1-ml injections of 5% Kollidon 17PF alone. Animals were examined daily, and body weight was recorded twice weekly. Fourteen days after the last taurolidine injection, mice in all of the groups were sacrificed, and all of the i.p. tumor foci were removed and weighed. The mean tumor weight for each treatment group was calculated, and statistical analysis of differences in the mean tumor weight used the Student t test. Ps of ≤0.05 were considered significant.

RESULTS

The ability of taurolidine to inhibit cell proliferation was assessed in a panel of human and murine neoplastic cell lines. This survey revealed that a 3-day exposure to taurolidine inhibited cell proliferation in each line examined (Table 1). The observed IC₅₀ values for individual cell lines were remarkably similar and ranged between 10 and 35 μM.

This observed inhibition of cell proliferation could reflect either growth arrest or death. Therefore, studies next focused on identifying the mechanism(s) by which taurolidine produced this effect. These studies were carried out in the human ovarian tumor cell lines PA-1 and SKOV-3 and in NIH-3T3 murine fibroblasts. In a preliminary study, taurolidine-containing media was replaced with fresh media after the 3-day incubation period. Under these conditions, cell proliferation resumed in NIH-3T3 cells within 1 week. In contrast, proliferation did not resume in either the PA-1 or SKOV-3 lines under these conditions. Next, studies assessed the effect of a 48-h exposure to taurolidine on cell cycle distribution and revealed that exposure to this agent did not induce a consistent pattern of cell cycle alterations.

In PA-1 cells, exposure to taurolidine exerted a variable effect on the percentage of cells in different phases of the cell cycle (Table 2). Alternatively, in SKOV-3 cells, taurolidine exposure resulted in a concentration-dependent decrease in the percentage of cells in G0/G1 but increased the percentage of cells in both the S-phase and G2-M phase.

### Table 1 The IC₅₀ of taurolidine against the growth of selected human and murine cell lines

<table>
<thead>
<tr>
<th>Tumor site of origin</th>
<th>Cell line</th>
<th>IC₅₀ (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovary</td>
<td>PA-1</td>
<td>11.4 ± 1.8</td>
</tr>
<tr>
<td></td>
<td>SKOV-3</td>
<td>31.6 ± 7.0</td>
</tr>
<tr>
<td>Prostate</td>
<td>DU-145</td>
<td>9.8 ± 0.8</td>
</tr>
<tr>
<td>Brain</td>
<td>U-251</td>
<td>20.1 ± 2.7</td>
</tr>
<tr>
<td>Colon</td>
<td>HT-29</td>
<td>18.6 ± 1.0</td>
</tr>
<tr>
<td></td>
<td>HCT-8</td>
<td>11.5 ± 0.5</td>
</tr>
<tr>
<td></td>
<td>HCT-15</td>
<td>9.6 ± 3.0</td>
</tr>
<tr>
<td>Melanoma</td>
<td>B16-F10</td>
<td>30.1 ± 2.6</td>
</tr>
<tr>
<td>Lung</td>
<td>MNT-1</td>
<td>22.1 ± 2.1</td>
</tr>
<tr>
<td></td>
<td>H-157</td>
<td>32.2 ± 5.6</td>
</tr>
<tr>
<td></td>
<td>A-549</td>
<td>26.8 ± 7.2</td>
</tr>
<tr>
<td></td>
<td>H-596</td>
<td>34.2</td>
</tr>
<tr>
<td>Murine fibroblasts</td>
<td>NIH-3T3</td>
<td>11.9 ± 1.8</td>
</tr>
</tbody>
</table>

Western blot analysis of PARP cleavage. Cells were seeded at a density of 1–5 × 10⁵ cells in each well of a 6-well tissue culture flask. Twenty-four h later, taurolidine was added at concentrations ranging from 1–100 μM. After 3 days, cells were harvested by trypsinization, and the cell number was determined. Cell growth inhibition was determined by comparison to non-taurolidine-exposed control cultures. The IC₅₀ was calculated as the concentration required to inhibit cell number by 50%. Each IC₅₀ value represents the mean ± SE of four to eight determinations.

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Fig. 1. Structure of taurolidine and its major breakdown products taurultam, taurinamide, and taurine. Upon breakdown, each molecule of taurolidine generates three methylol-containing fragments that have been suggested as being responsible for its antibiotic and antiendotoxin activities.
Table 2 The effect of a 48-h exposure to selected concentrations of taurolidine on cell cycle distribution in human ovarian tumor cells (PA-1 and SKOV-3) and murine fibroblasts (NIH-3T3)

Cells (3 x 10^5) were seeded in plastic tissue culture flasks. Twenty-four h later, taurolidine was added to achieve final concentrations of 25 μM, 50 μM, or 100 μM. Control cultures received an appropriate volume of Kollidine-17P. After an additional 48 h, cells were harvested and stained with propidium iodide, and cell cycle distribution was assessed using cytofluorometric techniques. Each value represents the percentage of cells in the noted cell cycle phases and is the mean ± SE of three determinations.

<table>
<thead>
<tr>
<th>Cell line/drug exposure</th>
<th>Sub G&lt;sub&gt;0&lt;/sub&gt;/G&lt;sub&gt;1&lt;/sub&gt;</th>
<th>G&lt;sub&gt;0&lt;/sub&gt;/G&lt;sub&gt;1&lt;/sub&gt;</th>
<th>S</th>
<th>G&lt;sub&gt;2&lt;/sub&gt;/M</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH-3T3 48 h-0 μM taurolidine</td>
<td>0.4 ± 0.2</td>
<td>6.1 ± 9.2</td>
<td>45.0 ± 5.9</td>
<td>9.0 ± 3.3</td>
</tr>
<tr>
<td>NIH-3T3 48 h-25 μM taurolidine</td>
<td>0.5 ± 0.2</td>
<td>42.5 ± 9.6</td>
<td>44.9 ± 5.6</td>
<td>13.0 ± 4.0</td>
</tr>
<tr>
<td>NIH-3T3 48 h-50 μM taurolidine</td>
<td>1.0 ± 0.2</td>
<td>33.9 ± 10.2</td>
<td>44.3 ± 5.9</td>
<td>21.8 ± 4.6</td>
</tr>
<tr>
<td>NIH-3T3 48 h-100 μM taurolidine</td>
<td>2.3 ± 0.9</td>
<td>25.8 ± 1.7</td>
<td>63.2 ± 9.8</td>
<td>11.0 ± 11.0</td>
</tr>
<tr>
<td>PA-1 48 h-0 μM taurolidine</td>
<td>1.2 ± 0.9</td>
<td>29.9 ± 1.5</td>
<td>47.7 ± 1.0</td>
<td>22.5 ± 0.5</td>
</tr>
<tr>
<td>PA-1 48 h-25 μM taurolidine</td>
<td>2.3 ± 0.5</td>
<td>28.4 ± 0.5</td>
<td>46.8 ± 0.6</td>
<td>24.7 ± 0.9</td>
</tr>
<tr>
<td>PA-1 48 h-50 μM taurolidine</td>
<td>19.4 ± 2.2</td>
<td>23.7 ± 2.2</td>
<td>39.5 ± 12.5</td>
<td>36.8 ± 12.4</td>
</tr>
<tr>
<td>PA-1 48 h-100 μM taurolidine</td>
<td>30.6 ± 1.4</td>
<td>28.4 ± 5.6</td>
<td>44.3 ± 23.5</td>
<td>27.2 ± 17.9</td>
</tr>
<tr>
<td>SKOV3 48 h-0 μM taurolidine</td>
<td>0.4 ± 0.1</td>
<td>46.7 ± 1.3</td>
<td>38.8 ± 4.1</td>
<td>13.5 ± 3.6</td>
</tr>
<tr>
<td>SKOV3 48 h-25 μM taurolidine</td>
<td>0.3 ± 0.3</td>
<td>45.8 ± 2.7</td>
<td>41.9 ± 4.2</td>
<td>12.3 ± 3.1</td>
</tr>
<tr>
<td>SKOV3 48 h-50 μM taurolidine</td>
<td>13.3 ± 6.0</td>
<td>30.7 ± 9.4</td>
<td>45.5 ± 12.4</td>
<td>30.3 ± 10.5</td>
</tr>
<tr>
<td>SKOV3 48 h-100 μM taurolidine</td>
<td>25.9 ± 7.8</td>
<td>19.9 ± 6.1</td>
<td>54.2 ± 8.6</td>
<td>25.9 ± 7.8</td>
</tr>
</tbody>
</table>

(Table 2). Significantly, in both ovarian tumor cell lines, taurolidine induced the appearance of DNA debris in the sub-G<sub>0</sub>/G<sub>1</sub> region in a concentration-dependent manner. Exposing NIH-3T3 cells to taurolidine decreased the percentage of cells in G<sub>0</sub>/G<sub>1</sub> and increased the percentage of cells in S in a concentration-dependent manner (Table 2). However, taurolidine did not significantly increase DNA debris in the sub-G<sub>0</sub>/G<sub>1</sub> region in these fibroblasts. Thus, in NIH-3T3 cells, taurolidine-induced growth arrest was associated with an increase in cells in S-phase.

DNA fragmentation, as observed in both PA-1 and SKOV-3 cells after taurolidine exposure, is an event that occurs relatively late in the apoptotic process. Thus, taurolidine could have induced apoptosis in these tumor cell lines. To evaluate this possibility, studies next assessed the ability of taurolidine to induce membrane phosphatidyserine externalization, an event that occurs earlier in apoptosis. The results of this study revealed that, in both the PA-1 and SKOV-3 tumor cell lines, a 24-h exposure to taurolidine induced a significant, concentration-dependent increase in annexin-V binding (Fig. 2). In contrast, in NIH-3T3 cells, taurolidine exposure resulted in a nonsignificant increase (~5%) in antibody binding. As an alternate assessment of apoptosis, the effect of taurolidine exposure on PARP cleavage also was monitored (34–38). Western-blot analysis was carried out on whole cell extracts of PA-1, SKOV-3, and NIH-3T3 cells after a 24-h exposure to either 50 or 100 μM taurolidine. Typical results of this analysis, presented Fig. 3, revealed that in PA-1 and SKOV-3 cells taurolidine exposure resulted in PARP cleavage. In contrast, there was little evidence of PARP cleavage after taurolidine exposure in NIH-3T3 fibroblasts.

Our findings that taurolidine appeared to induce apoptosis in human tumor cells suggested that this agent possessed antineoplastic activity. Studies to test this possibility were initiated in nude mice bearing human ovarian tumor xenografts. Initial studies were designed to identify the maximally tolerated dose of a 3-day i.p. bolus injection regimen. Daily injections delivered doses that ranged from 5 to 30 mg/mouse. The results of these studies revealed that doses below 15 mg/mouse/day (~650 mg/kg/day) were well tolerated (Table 3). Body weight loss as a result of these dose regimens was ≤7%, and body weight returned to preinjection levels within 7 days after the injection regimen. With regimens using doses of 20 mg/mouse/day or greater, more significant toxicity was observed (Table 3). Nadir weight loss for regimens using 20, 25, or 30 mg/mouse were −12%, −16%, and −25%, respectively. Additionally, these taurolidine-dose regimens resulted in 13%, 43%, and 100% mortality, respectively.

From these results, we selected the 20 mg/mouse/day regimen for evaluation of antineoplastic activity in mice bearing i.p. human ovar-
ian tumor xenografts derived from the SKOV-3 cell line. For these studies, mice received i.p. injections of 5 × 10^6 SKOV-3 cells. Taurolidine therapy was initiated up to 5 days after tumor cell injection. Fourteen days after the termination of therapy, mice were sacrificed, and tumors were removed and weighed. The results of this study revealed that, when initiated on the day of tumor cell injection, taurolidine therapy was highly effective and inhibited tumor formation (Fig. 4), ascites development, and growth (Fig. 5). Indeed, when therapy was initiated on the day of tumor cell injection, ~80% of treated mice had no evidence of disease upon sacrifice. Furthermore, the mean tumor size in treated mice was ~40-fold smaller than in control (vehicle-treated) mice. Equally impressive, if taurolidine therapy was delayed for up to 3 days after tumor cell injection, ~10% of mice were tumor-free upon sacrifice and the mean tumor size was again significantly smaller than in controls. Finally, the initiation of this single cycle of taurolidine therapy 5 days after tumor cell injection (Fig. 5), presumably in mice with established i.p. ovarian tumors, was still capable of inhibiting tumor growth, although no mice in this delayed treatment group were disease-free upon sacrifice.

**DISCUSSION**

In clinical use as a lavage antibiotic, taurolidine has been observed to be effective at concentrations in the low mM range, concentrations that can be obtained clinically without toxicity (4, 7, 17, 18). The data presented also reveal that this compound possesses antineoplastic activity, presumably reflecting its ability to induce apoptosis in the human ovarian tumor cell models used in this study. Surprisingly, the antiproliferative IC_{50} of taurolidine was found to be in the 10–50 μM range, approximately 100-fold lower that that required for its antibacterial effects. This difference in effective concentrations, combined with observed low clinical toxicities of taurolidine, suggests that this agent has an exploitable therapeutic index as an antineoplastic. This possibility combined with its unique structure and proposed mechanism of action (2, 8, 9, 17) supports the notion that taurolidine...
represents a novel class of anticancer agent that warrants further examination.

The present studies evolved from our hypothesis that taurolidine alone could disrupt the processes by which tumor cells adhere to other cellular surfaces, processes crucial for the development and growth of solid tumors. Indeed, our preliminary data revealed that exposure to taurolidine effectively inhibited the proliferation and viability of the ovarian tumor cell lines evaluated in our panel. Remarkable, however, were the results of our subsequent mechanism-based studies that revealed that exposure to taurolidine induced apoptosis in SKOV-3 and PA-1 human tumor cells but apparently not in NIH-3T3 fibroblasts. Clearly, this ability of taurolidine to induce programmed cell death suggests that its mechanism of action is not simply an inhibition of cell adhesion. Indeed, in our in vivo studies, mice with advanced tumors exposed to taurolidine were observed to contain tumors adhered to peritoneal surfaces. Further support of a mechanism other than a disruption of adherence has been obtained recently from results of studies we have carried out in nonadherent cancer cell models. These studies reveal that as little as a 90-min exposure to taurolidine induces apoptosis in the HL-60 human promyelocytic cell line (39). In these studies, we have also observed that exposure to taurolidine results in the activation of caspases 3, 8, and 9, a disruption of mitochondrial membrane integrity accompanied by cytochrome-c efflux from these organelles, and the cleavage of PARP protein (39, 40).

Surprising, however, is our observation that in Bcl2-overexpressing HL-60 cells, taurolidine exposure remains capable of inducing apoptosis, but with a delayed onset (41). An appealing possibility is that active taurolidine breakdown products are capable of reacting with membrane components to affect intracellular signaling processes and initiate the apoptosis process. It remains surprising that the ability of taurolidine to induce apoptosis appeared in our study to be specific for tumor cells. Indeed, although the proliferation of NIH-3T3 cells was inhibited by exposure to taurolidine, once this agent was removed, the proliferation of NIH-3T3 cells resumed. This resumption of proliferation was not observed in any of the tumor cell lines assessed in this study. We continue to investigate this selective cytotoxicity of taurolidine. Indeed, in recent studies carried out using normal murine bone marrow (40), concentrations in the mM range were required to inhibit cell proliferation. In these normal marrow cells also, once taurolidine was removed, both marrow proliferation and colony formation resumed (40). These findings may suggest that taurolidine or one of its metabolites accesses a tumor cell-specific target capable of inducing apoptosis. Unfortunately, detailed studies to assess the structure/activity relationship of taurolidine, particularly as it relates to the induction of cytotoxicity and/or apoptosis, are hampered by the rapid decomposition of taurolidine in aqueous environments combined with the inability, at the present time, of isolating and quantitating relevant intermediate metabolites.

In light of our observed ovarian tumor cell-specific activity and the relatively large therapeutic index of taurolidine, it is not surprising that the i.p. administration of taurolidine effectively inhibited the development and growth of i.p. ovarian tumors when therapy was initiated on the day of tumor cell injection. Indeed, studies by Jacobi et al. (42–44) revealed that the i.p. administration of a taurolidine-heparin-CO₂ mixture to rats that received simultaneous injections i.p. with DHD/K12/TRb colon adenocarcinoma cells prevented colon tumor cell adhesion. However, it was impressive that a single 3-day course of i.p. taurolidine therapy to mice with established i.p. ovarian tumors also effectively inhibited tumor growth. Studies are under way to develop a multiple cycle regimen of taurolidine for prolonged use in mice with advanced i.p. ovarian cancer. Concomitant murine-based studies also are under way to assess the efficacy of systemic taurolidine against the growth of s.c. human tumor xenografts (41).

In total, our results suggest that taurolidine possesses exploitable activity as an antineoplastic agent. Parallel with the progression of our preclinical studies, a comprehensive clinical evaluation of taurolidine in patients with ovarian cancer is under way. In this trial, taurolidine is administered by i.p. lavage immediately after surgery for removal of recurrent ovarian tumors. Also initiated is a clinical trial to evaluate the toxicity and efficacy of i.v. taurolidine in patients with glioblastoma. Although it is premature to assess efficacy, preliminary results do reveal that taurolidine is well tolerated in these clinical settings. Clearly, additional laboratory and clinical studies to assess the antineoplastic activity of taurolidine are warranted.

### References


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