The Effects of Taurolidine, a Novel Antineoplastic Agent, on Human Malignant Mesothelioma

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ABSTRACT

Purpose: Malignant mesothelioma (MM) is a cancer with uniformly poor responses to current therapeutic regimens. This study evaluates whether taurolidine, a novel antineoplastic agent, is effective against human MM cell lines and a murine model of human MM.

Experimental Design: Cell growth inhibition and viability assays were performed on REN, LRK, and H28 cell lines after 24–72-h exposure to 0–200 μM taurolidine. Cell cycle analysis with annexin-V binding, terminal deoxynucleotidyl transferase-mediated nick end labeling assay, electron microscopy, and response to the general caspase inhibitor z-VAD-fmk were performed on MM cell lines after 24–72-h exposure to 50–150 μM taurolidine. Athymic mice were given i.p. injections of 20 × 10⁶ REN cells, followed by i.p. taurolidine (17.5 or 20 mg), 3 days/week for up to 3 weeks. Tumors were assessed at day 30. All statistical tests were two-sided.

Results: A 72-h exposure of MM cells to taurolidine showed IC₅₀ of 28–42.7 μM and 50% viability at 49.8–135 μM. Annexin V assay for apoptosis revealed significant increases in annexin binding after 24–72-h exposure to 50–150 μM taurolidine (P < 0.05), which was significantly inhibited by z-VAD (P < 0.05). MM cells exposed to 50–150 μM taurolidine for 24–72 h showed terminal deoxynucleotidyl transferase-mediated nick end labeling staining consistent with apoptosis, as well as structural evidence of apoptosis via electron microscopy. In vivo, there were significant tumor reductions (62 to >99% reduction) for all dosage regimens compared with untreated controls (P < 0.001). In addition, all control animals exhibited ascites and diaphragmatic tumors while treated animals did not.

Conclusions: Taurolidine has significant antineoplastic activity against MM in vitro and in vivo, in part, due to tumor cell apoptosis. These findings warrant further study for potential clinical usefulness.

INTRODUCTION

Approximately 4000 new cases of malignant mesothelioma (MM) are diagnosed in the United States each year, with an expected peak during the next decade (1). MM, a rare cancer whose development is strongly associated with asbestos exposure, is characterized by a long latency period. The tumor is highly resistant to traditional chemotherapy and radiation therapy. Surgical resection carries a high morbidity and low curative rate. Patients diagnosed with MM have an average survival of 6–18 months and virtually 100% mortality within 5 years (2).

Resistance to apoptosis may be important both for the initial development and for the continued survival of tumors (3, 4). An initial resistance to apoptosis may be necessary to allow the amplification of a population of abnormal cells, and a continued resistance to apoptosis may underlie the insensitivity of tumor cells to chemotherapy and radiotherapy. Indeed, resistance to apoptosis could explain MM’s striking insensitivity to traditional therapy. Asbestos fibers cause apoptosis of normal mesothelial cells; however, mesothelioma cell lines are resistant to apoptosis due to exposure to asbestos fibers, H₂O₂, and calcium ionophore (5). This resistance to apoptosis is not affected by the presence of p53, and Bcl-2 is not overexpressed in mesothelioma cells. In fact, most mesothelioma cell lines contained Bax, therefore, having a low Bcl/Bax ratio that is typically associated with favorable histological grade and responsiveness to treatment.

Taurolidine, originally synthesized in the 1970s, is chemically identified as Bis-[(1,1-dioxopiperhydro-1,2,4-thiadiazinyl-4)-methane (6). It is a small dimeric molecule with a molecular weight of 284. It is bactericidal against a broad range of aerobic and anaerobic bacteria and also possesses antifungal activity (7). Taurolidine has also been used clinically to reduce the extent and severity of postoperative peritoneal adhesions (8). Interestingly, Jacobi et al. (9) reported that i.p. taurolidine inhibits adherence of colon tumor cells injected into the peritoneal cavity of rats. More recent evaluations of taurolidine have shown significant antineoplastic activity in several human tumor cell lines in vitro, as well the ability to decrease tumor burden in a murine model of i.p. human ovarian carcinoma (10). These data led to the current studies, which examine taurolidine’s activity against three human MM cell lines in vitro and in human MM xenografts in athymic mice. We now report that taurolidine causes significant in vitro growth inhibition and cytotoxicity of human MM cells, which appears to be due, at least in part, to apoptosis. In addition, we show that taurolidine is able to significantly reduce the growth and spread of human MM in the peritoneal cavities of immunosuppressed mice. These data warrant further study of this compound for potential clinical effectiveness in MM.
MATERIALS AND METHODS

Reagents. Taurolidine was generously provided by Carter Wallace, Inc. (Cranbury, NJ), as a 2% solution in 5% Kollidon 17PF. Appropriate cell culture growth medium (RPMI 1640), trypsin, and fetal bovine serum were purchased from Life Technologies, Inc. (Grand Islip, NY). Pan-caspase inhibitor zVAD-fmk was purchased from R&D Systems, Inc. (Minneapolis, MN). Apo-alert annexin V kit was purchased from Clon- tech Laboratories (Palo Alto, CA). Terminal deoxynucleotidyl transferase-mediated nick end labeling (TUNEL) assay was performed using the in situ cell death detection kit from Boehringer Mannheim Corp. (Indianapolis, IN).

Cell Lines. Studies to assess the cytotoxic activity of taurolidine were carried out on three human MM-derived cell lines. REN and LRK [gift of Dr. Steven Albelda, University of Pennsylvania, Philadelphia, PA] containing abnormal p53 resulting in an absence of p53 protein and H28 (American Type Culture Collection, Manassas, VA). Cells were carried in the appropriate medium (RPMI 1640) with supplements and 10% FCS at 37°C in a humidified incubator in an atmosphere of 5% CO2. Under these growth conditions, the doubling time of the cell lines was 24–36 h (REN and LRK) and 36–48 h (H28).

Animals. All studies to assess in vivo toxicity and therapeutic effectiveness were carried out in 6- to 8-week-old male, beige, nude, xid mice obtained from Harlan Sprague Dawley (Indianapolis, IN). All animal care was in accord with institutional guidelines.

Cell Growth Inhibition Assays. Subconfluent monolayers of MM cells were harvested by trypsinization and resuspended in media at a cell density of 1–5 × 10^5 cells/ml. One ml of this cell suspension was added to each well of a 12-well cell culture plate that contained 1 ml of appropriate media plus serum. Taurolidine was then added in a volume of 20 μl to each well to achieve a final concentration of 0.1–200 μM. Control wells received 20 μl of 5% Kollidon 17PF alone. Seventy-two h later, all cells were harvested by trypsinization and cell number determined electronically using a Coulter Model Z1 particle counter (Coulter Corp., Miami, FL). Each experiment was performed in duplicate and repeated a minimum of three times.

Cell Viability Assays. Subconfluent monolayers of MM cells were harvested by trypsinization and resuspended in media at a cell density of 1 × 10^6 cells/ml. Taurolidine concentrations (0–200 μM) were prepared in 950 μl of media. Fifty μl of the cell suspension were added for a final cell concentration of 5 × 10^5 cells/ml. Two-hundred μl of each concentration of taurolidine and cells were placed in triplicate in 96-well plates and incubated for 72 h. Fifty μl of 0.2% 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide were then added to each well and allowed to incubate for 4 h. Plates were centrifuged and the supernatant aspirated. A total of 150 μl of DMSO was added to each well to dissolve the crystals that had formed. The plates were then read on a spectrophotometer at a wavelength of 550. The mean of each taurolidine concentration was compared with the mean of the untreated control to determine percent viability.

Cell Membrane Phosphotidylserine Externalization. Cell membrane phosphotidylserine externalization (a reflection of the potential induction of apoptosis) was assessed by flow cytometry using ApoAlert Annexin-V/FITC assay kit (Clontech Laboratories). Briefly, 1 × 10^6 cells were incubated for 24 h in appropriate media containing serum. Taurolidine was then added to achieve a final concentration of 50, 75, 100, or 150 μM. Control cultures received vehicle alone. Twenty-four, 48, and 72 h later, cells were harvested by trypsinization and resuspended in 200 μl of binding buffer and then incubated for 5–15 min in a 1 μg/ml Annexin-V/FITC solution at room temperature in the dark. The cells were then analyzed to quantitate Annexin-V binding by cytofluorometric techniques that used FACScan (Benton Dickinson, Plymouth, United Kingdom) using the ModFit LT program. Statistical analysis was performed with the Kruskal-Wallis nonparametric ANOVA test followed by Dunn’s multiple comparisons test using Instat.

The role of caspase activation in this process was studied by the addition of the pan-caspase inhibitor zVAD-fmk. ZVAD-fmk (0–50 μM) was added to cultured MM cells 2 h before the addition of taurolidine (final concentration, 50–150 μM). The annexin assay was then completed as described above.

TUNEL Assay. MM cells were grown on Lab-Tek Chamber slides and exposed to 50–150 μM taurolidine for 24–48 h. Cells were fixed with fresh 4% formaldehyde/PBS at 4°C for 25 min, then permeabilized with prechilled 0.2% Triton X-100/PBS. TUNEL assay was then performed according to manufacturer’s instructions. Apoptotic nuclei were identified by the presence of green fluorescent staining. The apoptotic index was expressed as the percentage of positive nuclei for 100 counted cells at magnification of ×100.

Electron Microscopy. MM cells were grown on Nunc Permanox 60-mm plates and exposed to 50–150 μM taurolidine for 72 h. Cells were initially fixed in 1.0% glutaraldehyde in 0.1 M sodium cacodylate buffer (pH 7.2) and then postfixed in cacodylate-buffered 1% osmium tetroxide. Cells were then dehydrated in ethanol, embedded in Spurr’s resin, and sectioned at 50 nm for electron microscopy. Sections were stained in uranyl acetate and lead citrate and examined in a Philips 300 transmission electron microscope for evidence of apoptosis.

Statistical Methods. All assays were performed in triplicate and expressed as mean values +/- SE. Statistical differences among groups were determined by the Student’s t test. All tests of statistical significance were two-sided. P values of <0.05 were considered significant.

In Vivo Evaluation of Toxicity and Therapeutic Effectiveness. To evaluate potential taurolidine-induced toxicity, mice were divided into groups of 6–12 animals. All mice were then weighed and given single i.p. injections of taurolidine on three consecutive days/week at 17.5, 20, or 30 mg/mouse/injection in a maximum volume of 1 ml. Control animals received 1-ml injections of 5% Kollidon 17PF alone. Animals were examined daily and body weights recorded twice weekly. A reduction in body weight of >10% was considered significant. The maximum-tolerated dose was considered to be the dose which produced ~10% mortality.

To evaluate the therapeutic effectiveness of taurolidine against human MM, mice received a single i.p. injection of 20 × 10^6 REN cells in a volume of 1 ml of serum-free media. Initial studies were performed to evaluate the natural history of tumor progression and survival. In these studies, two to four mice were sacrificed each week and tumor spread and bulk recorded. Five animals were followed until death from tumor. In the next series...
of experiments, mice were randomly divided into treatment groups of 10 animals. Day 1 is noted as the day after tumor inoculation. Taurolidine therapy was initiated as follows: (a) single i.p. bolus injection of 20 mg of taurolidine on days 1, 2, and 3 for week 1 only; (b) single i.p. bolus injection of 17.5 mg of taurolidine on days 1, 2, and 3 for weeks 1–3; (c) single i.p. bolus injection of 17.5 mg of taurolidine on days 1, 2, and 3 for weeks 2–4; (d) single i.p. bolus injection of 20 mg of taurolidine on days 1, 3, and 5 for weeks 1–3; (e) single i.p. bolus injection of 20 mg of taurolidine on days 1, 3, and 5 for weeks 2–4; and (f) control untreated animals with tumor. Animals were examined weekly and weights recorded. Animals were sacrificed by CO2 asphyxiation on day 30 post-tumor instillation, and all tumor foci were removed and total tumor weight determined. In addition, the presence and volume of ascites were recorded, and gross tumor involvement of the diaphragm was noted in each animal. The mean tumor weight for each treatment group was calculated, then we used Student’s t test for statistical analysis of differences in the mean tumor weight between treatment groups. P values of <0.05 were considered significant.

RESULTS

The ability of taurolidine to inhibit cell growth was assessed for REN, LRK, and H28 cell lines. A 3-day exposure to taurolidine inhibited the growth of REN cells with IC50 of 42.7 μM, LRK cells with IC50 of 28 μM, and H28 cells with IC50 of 30.8 μM. The cytotoxic effect of taurolidine was assessed by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay, which showed a 50% viability at 135 μM (REN), 50 μM (LRK), 49.8 μM (H28), after a 3-day exposure to taurolidine (Fig. 1). Studies were next undertaken on the REN and LRK cell lines to define the mechanism(s) by which taurolidine induced growth arrest and cytotoxicity.

Conventional flow cytometry techniques were used to assess the ability of 0–150 μM taurolidine to increase phosphotidylserine externalization on MM cell membranes, an early event in apoptosis. Fifty to 150 μM taurolidine exposure for 24–72 h induced a significant increase in annexin-V binding, consistent with apoptosis of both MM cell lines (Fig. 2). The role of caspase activation was evaluated in this process by addition of zVAD, a pan-caspase inhibitor, 2 h before treatment with taurolidine. Annexin-V binding was significantly inhibited in both cell lines by the presence of zVAD, consistent with a caspase-dependent pathway of apoptosis (Fig. 3).

As an alternate assessment of apoptosis, we evaluated the ability of taurolidine to induce DNA fragmentation. TUNEL assay was carried out on MM cells after 24–48-h exposure to 50–150 μM taurolidine (Fig. 4). Exposure to taurolidine resulted in significant increases in positive TUNEL-staining cells [apoptotic index: 35.1 ± 4.3 (REN); 43 ± 6.2 (LRK)], consistent with apoptosis compared with untreated control cells (apoptotic index: 4.1–6.5). Electron microscopy was also performed on MM cells after exposure to taurolidine. After a 72-h exposure to 50–150 μM taurolidine, MM cells were noted to have lobulated nuclei, abnormal chromatin aggregates, and budding cell fragments with intact organelles, all consistent with early apoptosis (Fig. 5).
In light of our in vitro findings that taurolidine induces growth inhibition and cytotoxicity in human MM cell lines, in part via apoptosis, we next investigated if taurolidine would possess antineoplastic activity in vivo. Initial studies were undertaken to document tumor progression and survival in a murine model of i.p. human MM. Fifteen days after 20 × 10⁶ REN cells were injected into the peritoneal cavity of immunosuppressed (xid) mice, small peripancreatic masses were noted in ~50% of subjects. On day 22, all mice had peripancreatic tumors, and >50% had two to three small mesenteric tumor nodules. Day 28 revealed consistently large peripancreatic tumors (1–1.5 cm), multiple mesenteric nodules, and ~75% incidence of bloody ascites and diaphragmatic involvement. On days 30–35, there were very large, bulky peripancreatic tumors (2–2.5 cm) extending to the lesser curvature of the stomach, numerous large mesenteric tumor nodules, large amounts of bloody ascites, and bulky diaphragmatic involvement in >95% of animals. Animals expired on day 68 (mean) (range, 63–74 days).

Intraperitoneal bolus injections of taurolidine were given to immunosuppressed mice to identify the maximum-tolerated dose regimen and assess toxicity of the compound as judged by changes in body weight and mortality. Daily 1-ml injections of 17.5, 20, or 30 mg/mouse/day were delivered for 3 consecutive days. Daily doses of 17.5 and 20 mg/mouse/day for 3 consecutive days over 4 weeks were well tolerated with no significant weight loss and mortality <10%. Three daily injections of 30 mg/mouse/day resulted in significant mortality of 40% after 1 week. Given these results, we chose to deliver 17.5–20 mg/mouse/day to mice bearing i.p. human MM xenografts in various regimens. The results of these studies are summarized in Tables 1 and 2. Representative pictures of the tumor model are also displayed (Figs. 6 and 7). All taurolidine regimens were effective in reducing overall tumor formation, including total

**Fig. 3** Evidence of caspase-dependent apoptosis induced by taurolidine. REN (A) and LRK (B) cells were exposed to 150 or 50 μM taurolidine, respectively (or vehicle alone), for 48 h either with or without zVAD-fmk (25–40 μM) given 2 h earlier. zVAD significantly reduced annexin V staining in response to taurolidine. Each bar represents the mean of four determinations; *, P < 0.05.

**Fig. 4** Terminal deoxynucleotidyl transferase-mediated nick end labeling assay in REN cells (A, untreated; B, 150 μM taurolidine for 48 h) and LRK cells (C, untreated; D, 50 μM taurolidine for 24 h). Representative micrographs (∼100 magnification) are shown. Terminal deoxynucleotidyl transferase-mediated nick end labeling assay was performed according to manufacturer’s instructions. Apoptotic nuclei are identified by the presence of bright pinpoint nuclear staining.
**DISCUSSION**

MM is a localized tumor of the pleural or peritoneal cavity, which is closely associated with asbestos exposure. Despite the banning of asbestos in the United States > 25 years ago, this neoplasm continues to be diagnosed due to a long latency period between exposure and clinical disease. In fact, incidence of MM in the United States is expected to rise over the next decade due to this long latent period (1). Furthermore, in countries such as Italy, Australia, and South Africa, incidence of this malignancy is much higher than in the United States because of more recent asbestos exposure, abandoned mines, and inadequate occupational protection guidelines. In fact, epidemiological studies predict that up to a quarter of one million Europeans will develop MM during the next few decades (11). There is currently no effective treatment for mesothelioma, and most patients succumb to the disease within 2 years of diagnosis (2). In this article, we provide evidence that taurolidine, a synthetic antibiotic, has significant antineoplastic activity against MM both in vitro and in vivo and that this effect is due, at least in part, to tumor cell apoptosis.

Taurolidine, when used as a peritoneal lavage antibiotic, is effective at low mM concentrations without significant clinical toxicity (8). In our in vitro studies using three human MM cell lines, we see potent growth inhibition and cytotoxicity at mM concentrations, which are ~100-fold lower than that used for antibiotic effect. These significantly lower doses needed for antitumor effect and the lack of significant toxicities make taurolidine a very attractive candidate for use as an antineoplastic agent.

Studies evaluating the mechanism of this growth inhibition are consistent with the induction of apoptosis. MM cells show externalization of phosphotidylserine on cell membranes by 48 h of taurolidine exposure, and DNA fragmentation and electron microscopy structural changes are consistent with apoptosis after 48–72 h of taurolidine exposure. In addition, the pan-caspase inhibitor, zVAD, was able to significantly inhibit annexin binding of MM cells after taurolidine exposure. These findings are all consistent with caspase-dependent apoptosis of these cells in response to taurolidine. The ability of taurolidine

<table>
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<tr>
<th>Dosage regimen*</th>
<th>% mortality</th>
<th>% with tumor</th>
<th>% with ascites</th>
<th>% with diaphragm tumor</th>
<th>Body weight (g)</th>
<th>Tumor weight (mg)</th>
<th>% decrease tumor size from control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated tumor</td>
<td>0%</td>
<td>100%</td>
<td>80 +/- 70%</td>
<td>100%</td>
<td>26.3 +/- 1.5</td>
<td>171.6 +/- 113</td>
<td>80%†</td>
</tr>
<tr>
<td>20 mg/mouse/injection (days 1–3, week 1)</td>
<td>&lt;10%</td>
<td>80 +/- 7%</td>
<td>80 +/- 10%</td>
<td>100%</td>
<td>23.6 +/- 1.0</td>
<td>33.3 +/- 47</td>
<td>80%†</td>
</tr>
<tr>
<td>17.5 mg/mouse/injection (days 1–3, weeks 1–3)</td>
<td>&lt;10%</td>
<td>40 +/- 15%</td>
<td>-0-</td>
<td>-0-</td>
<td>23.1 +/- 2.0</td>
<td>2.9 +/- 4</td>
<td>&gt;98%†</td>
</tr>
<tr>
<td>17.5 mg/mouse/injection (days 1–3, weeks 2–4)</td>
<td>&lt;10%</td>
<td>100%</td>
<td>-0-</td>
<td>-0-</td>
<td>23.1 +/- 2.0</td>
<td>65.5 +/- 88</td>
<td>62%†</td>
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</table>

* Groups of 10 mice received i.p. injections of 20 × 10⁶ REN human malignant mesothelioma cells. The following day, therapy was begun with i.p. taurolidine (17.5 or 20 mg/mouse/injection) given on 3 consecutive days for 1 week or weeks 1 through 3 or weeks 2 through 4. All experiments were repeated a minimum of three times.
† All treated animals had statistically significant decreases in tumor weight compared to untreated tumors using the Student’s t test.
to induce apoptosis appears to be specific for tumor cells. Although NIH-3T3 cells are growth inhibited by this compound at a dose of 100 \( \mu \)M, proliferation resumes once the compound is removed (10). Exposure of normal murine bone marrow cells to much higher concentrations (1–10 mM) of taurolidine only slightly reduced the total number of viable cells recovered 21 days after exposure, whereas viable cells were completely eliminated from neoplastic cultures (12). Our findings appear to be even more striking in that mesothelioma cell lines have been shown to be exquisitely resistant to apoptosis from a number of conventional stimuli, including hydrogen peroxide, asbestos fibers, and calcium ionophore (5). It has been postulated that this resistance to apoptosis may explain the resistance of this tumor to chemotherapeutic agents and radiotherapy.

The mechanisms by which taurolidine induces apoptosis have not been elucidated. One possible mechanism for this effect may be taurolidine’s displacement or depletion of normal taurine levels in neoplastic cells. The conditionally semisessential amino acid taurine possesses a number of cytoprotective properties through its actions as an antioxidant, osmoregulator, and intracellular Ca\(^{2+}\) flux regulator (13). Taurine has been shown to reduce the cell damage associated with the ischemia-reperfusion phenomena, to provide protection against interleukin 2-induced lung injury, and to attenuate adhesion of leukocytes to endothelial cells (14–16). Redmond et al. (17, 18) has shown that taurine prevents apoptosis of human neutrophils and rat hepatocytes. Taurine has also been recently shown to prevent endothelial cell apoptosis due to a variety of causes, including high glucose, smoking, and shear stress (19, 20). If taurolidine interrupts normal taurine uptake by neoplastic cells, this may induce apoptosis of these cells. However, there would need to be significant differences in uptake/metabolism between neoplastic and nonneoplastic cells to explain taurolidine’s exclusive effects on neoplastic cells. Future studies, including ones in which supplemental taurine is provided during taurolidine therapy, may begin to provide insight into possible mechanisms. These questions clearly deserve further intensive study.

In conclusion, taurolidine is cytotoxic to three human MM

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**Table 2** Effects of various taurolidine dosage regimens on development of I.P. human malignant mesothelioma in athymic (xid) mice

<table>
<thead>
<tr>
<th>Dosage regimen*</th>
<th>% mortality</th>
<th>% with tumor</th>
<th>% with ascites</th>
<th>% decrease tumor size from control</th>
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<tr>
<td>Untreated tumor</td>
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<td>100%</td>
<td>100%</td>
<td>28.6 +/- 1.5</td>
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<tr>
<td>20 mg/mouse/injection (days 1, 3, and 5 for weeks 1–3)</td>
<td>0-</td>
<td>14 +/- 15%</td>
<td>0-</td>
<td>22.1 +/- 2.2†</td>
</tr>
<tr>
<td>20 mg/mouse/injection (days 1, 3, and 5 for weeks 2–4)</td>
<td>0-</td>
<td>50 +/- 6%</td>
<td>0-</td>
<td>20.0 +/- 3.0†</td>
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</table>

* Groups of 10 mice received i.p. injections of 20 \( \times 10^6 \) REN human malignant mesothelioma cells. The following day, therapy was begun with i.p. taurolidine (20 mg/mouse/injection) given on Monday, Wednesday, and Friday for weeks 1 through 3 or weeks 2 through 4. All experiments were repeated a minimum of three times.

† All treated animals had statistically significant lower weights compared with untreated controls.

‡ All treated animals had statistically significant decreases in tumor weight compared with untreated tumors using the Student’s \( t \) test.

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**Fig. 6** Representative photograph of tumor involvement of the diaphragm in mice bearing i.p. xenographs of REN human malignant mesothelioma cells. Mice were transected below the diaphragm on day 35 after i.p. tumor cell instillation, and the abdominal surface of the diaphragm was photographed. A, control mouse showing gross tumor involvement of the diaphragm; B, mouse treated with 20 mg of taurolidine on days 1, 3, and 5 for weeks 1–3. There is no observable tumor on the abdominal surface of the diaphragm; C, mouse treated with 20 mg of taurolidine on days 1, 3, and 5 for weeks 2–4. There is no observable tumor on the abdominal surface of the diaphragm.
It also appears to be highly effective in inhibiting growth and development of human MM in immunocompromised mice. The most effective dosing was given 1 day after tumor instillation and continued for 3 weeks; however, significant tumor inhibition also occurred when therapy was given for a single week or was delayed for a week. Interestingly, all treatment regimens showed a striking absence of ascites and gross diaphragmatic tumor involvement. Additional elucidation of taurolidine’s mechanism(s) of action and its clinical efficacy are necessary. The results presented here are compelling for the potential role of taurolidine in the treatment of MM, a uniformly fatal human neoplasm.

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We thank Carter-Wallace for providing the taurolidine used in this study.

REFERENCES

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