Chemosenstization of L-Phenylalanine Mustard by the Thiol-modulating Agent Buthionine Sulfoximine

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**ABSTRACT**

Glutathione (GSH) plays a crucial role in the protection of normal and normal tissue against the toxic effects of numerous chemotherapeutic drugs. Therefore, the possible therapeutic benefit of thiol depletion in cancer treatment is dependent upon the relative degree to which tumor or normal tissue is sensitized to the toxic effects of subsequent chemotherapy. To address this issue, the following studies on the chemosensitization of melphalan (L-PAM) by the thiol-depleting agent buthionine sulfoximine (BSO) were conducted in vivo in BDF mice inoculated with L-PAM-resistant murine L1210 leukemia. Different dosing regimens of BSO were found to potentiate L-PAM toxicity in a manner that depended upon the degree of GSH depletion. Multiple i.p. injections of BSO (450 mg/kg every 6 h x 5) were found to reduce GSH concentrations in most tissues by 70–80%, and to decrease the LD₅₀ for L-PAM from 22 to 14 mg/kg. No two organs were found to behave entirely the same with respect to the rate of depletion or recovery of GSH, or to the maximum depletion or recovery. BSO was found to be the most resistant tissue to thiol depletion by BSO and was found to tolerate the combination of BSO and therapeutic doses of L-PAM. However, BSO pretreatment markedly inhibited the recovery of the peripheral WBC population at the LD₅₀ dose of L-PAM. Differences also were found in the in vivo metabolism of GSH by L-PAM-sensitive and -resistant murine L1210 leukemia cells. The intracellular concentration of GSH in the resistant cell line was 1.6-fold higher than in the sensitive tumor. Moreover, GSH levels were depleted more rapidly in the resistant tumor relative to the sensitive cell line. A single injection of BSO decreased GSH concentrations in both tumors to equivalent levels (20 nmol/10⁷ cells) within 24 h. However, multiple i.p. injections of BSO failed to produce a significant increase in the life-span of L-PAM-treated animals despite a 90% reduction in tumor GSH concentrations (5.5 nmol/10⁷ cells). In contrast to the median day survival data, BSO was found to enhance the antitumor activity of L-PAM as determined by an in vivo / in vitro clonogenic assay or by in vivo thymidine incorporation. Using decreased thymidine incorporation as an index of antitumor activity, BSO was found to increase the therapeutic index (LD₅₀/ED₅₀) of L-PAM from 3.6 to 6.5. The present findings provide the first indication that tumor tissue may be more sensitive than normal tissue to L-PAM toxicity following GSH depletion and suggests that thiol modulation by BSO may be useful as an adjuvant in cancer chemotherapy.

**INTRODUCTION**

GSH, has been shown to play a crucial protective role against cellular injury produced by a number of toxic insults including ionizing radiation (1), reactive electrophiles (2, 3), and reactive oxygen intermediates generated by the respiratory burst of phagocytes (4) or the metabolism of quinone-containing drugs (5). The importance of GSH in mediating the therapeutic occupancy or chemotherapy is directly related to its role in cellular defense and is the subject of a recent review (6).

Interest in the possible use of thiol-modulating agents in cancer chemotherapy has been stimulated by several recent developments including studies in human and in rodent tumor cell lines which have shown that resistance to alkylating agents may, in certain instances, be due to elevated tumor GSH concentrations. For example, human ovarian and murine L1210 cancer cell lines with acquired resistance to L-PAM were shown to have elevated GSH concentrations (7, 8). Similar findings were obtained from ovarian cancer cell lines derived from patients who were clinically resistant to alkylating agents (7). The resistance of the above cell lines to L-PAM was reversed by depletion of cellular GSH (7, 8). A second factor which has stimulated interest in thiol modulation has been the development of an agent that can selectively inhibit the rate-limiting enzyme in GSH biosynthesis, thereby depleting tissues of GSH (9). In this regard, buthionine sulfoximine has been shown to have little pharmacological activity other than inhibition of GSH biosynthesis (9–11), and is well tolerated under experimental conditions (9, 12, 13).

Depletion of cellular GSH by BSO has been shown to sensitize tumor cells to irradiation (12–14) and to certain chemotherapeutic agents in vitro (7, 15–17). Such studies have led to a growing interest in the use of BSO as a chemosensitizer in cancer chemotherapy and its clinical application is currently under development at the National Cancer Institute. However, GSH may also play a similar role in the protection of normal tissue against the toxic effects of chemotherapeutic drugs. In this regard, BSO has been shown to potentiate the renal toxicity of MeCCNU and to result in a hepatotoxicity that was not ordinarily seen when MeCCNU was administered alone (18). Therefore, treatment strategies involving GSH depletion should take into consideration the possible effect that GSH depletion may have on the tissue sensitivity and target organ specificity of the anticancer agents that are to be used in combination with compounds such as BSO.

In this regard, the following studies on the chemosensitization of L-PAM by BSO were conducted in vivo, in mice bearing L-PAM-sensitive and -resistant murine L1210 leukemia. In these studies, various dosing schedules of BSO were compared for their ability to deplete tumor and normal tissue GSH concentrations in an attempt to maximize the therapeutic efficacy of the BSO/L-PAM combination.

**MATERIALS AND METHODS**

Male BDF mice (22–25 g) obtained from the Frederick Cancer Research Facility (Frederick, MD) were maintained in a temperature, humidity, and light controlled environment throughout the study. BSO (Chemical Dynamics Corp., South Plainfield, NJ) was administered either as a single (2 mM; 450 mg/kg) or by multiple i.p. injections (450 mg/kg every 6 h x 4). In some experiments, BSO was administered in the animals’ drinking water (20 mM). Animals that had received BSO in their drinking water consumed approximately 2 ml/day/mouse (i.e., 40 μmol/mouse). L-PAM was provided by the Pharmaceutical Resources Branch, National Cancer Institute. A 30-mm stock solution of L-PAM was prepared in dimethyl sulfoxide.

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2 The abbreviations used are: GSH, glutathione; L-PAM, L-phenylalanine mustard; BSO, buthionine sulfoximine; PBSA, Dulbecco’s phosphate buffered saline; MIF, multiple i.p. injection; H₂[¹⁴]Tdr, [methyl-⁴]thymidine; LD₅₀, dose lethal to 10% of animals; ED₅₀, dose which produces a 50% inhibition of [methyl-⁴]thymidine incorporation in vivo; MeCCNU, 1-(2-chloroethyl)-1-(methyl-⁴)thymine; MeSO, dimethyl sulfoxide; WBC, white blood cells.

3 The abbreviations used are: GSH, glutathione; L-PAM, L-phenylalanine mustard; BSO, buthionine sulfoximine; PBSA, Dulbecco’s phosphate buffered saline; MIF, multiple i.p. injection; [H]Tdr, [methyl-³]thymidine; LD₅₀, dose lethal to 10% of animals; ED₅₀, dose which produces a 50% inhibition of [methyl-³]thymidine incorporation in vivo; MeCCNU, 1-(2-chloroethyl)-1-(methyl-³)thymine-1-nitrosourea.
CHEMOSENSITIZATION OF L-PAM BY BSO

RESULTS

GSH Depletion. A single dose of BSO depleted GSH concentrations in all tissues examined (Fig. 1). However, no two organs behaved entirely the same with respect to the rate of depletion, or recovery of GSH, or the maximal depletion that was obtained. For example, kidney and liver GSH levels were maximally depleted within 2 h; however, renal GSH remained fully depleted at 24 h whereas liver GSH had returned to control values. The concentration of GSH in the heart also was markedly depleted at 24 h but required a much longer time to achieve maximum depletion (8 h, versus 2 h for kidney). These differences in the initial rate of GSH depletion reflect the rate of GSH utilization, or turnover of GSH, in a given tissue. In this regard, the lung appeared to turnover GSH only very slowly as reflected by the estimated biological half-life for GSH in the lung of 7.5 h. This compares to the estimated half-life for GSH in the liver and the kidney of 1.5 h. Bone marrow was found to have extremely low cellular concentrations of GSH (7 nmol/10^7 cells) and to be the most refractory to GSH depletion by BSO (Fig. 2). The maximal depletion that was obtained in bone marrow was only 20%. This compares to a 55% decrease in the lung or to the 70–80% decrease that was observed in the liver, kidney, heart, or stomach.

Differences also were found in the metabolism of GSH by L-PAM-resistant (L1210R) and -sensitive murine L1210 leukemia cells (Fig. 2). The intracellular concentration of GSH in L1210 cells was 1.6-fold higher than in the sensitive cell line. Moreover, GSH levels were depleted more rapidly in the resistant murine leukemia relative to the sensitive tumor. Such differences in the rate of GSH depletion may be due to differences in the rate of utilization or synthesis of GSH, or to differences in the uptake or retention of BSO by the resistant and sensitive tumor cell lines, respectively. However, GSH concentrations in both tumors were maximally depleted 24 h after BSO administration. At this time, GSH concentrations were equal in both cell lines (i.e., 20 nmol/10^7 cells).

Several different chronic dosing models for thiol depletion by BSO also were investigated (Fig. 3). MIPs of BSO (450 mg/kg every 6 h × 5) resulted in a greater decrease in tissue GSH concentrations compared to an oral dosing regimen (p.o.) which consisted of a single i.p. dose of BSO (450 mg/kg) followed by 3 days of feeding BSO in the animals’ drinking water (approx-

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**Fig. 1.** Time-course for depletion and recovery of tissue GSH concentrations after a single i.p. injection of BSO (450 mg/kg). Values are expressed as a percentage of time-matched controls. Each value is the mean of five animals; standard errors were less than 10% of the respective means.
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Fig. 2. Time-course for depletion of GSH concentrations in bone marrow and in L-PAM-sensitive and -resistant murine L1210 leukemia cells after a single i.p. injection of BSO (450 mg/kg). L1210 cells were harvested from animals as described in "Materials and Methods" and GSH levels are expressed as the mean ± SE of five animals. A total of six nontumored animals per time point were used for determining bone marrow GSH levels. Each value is the mean of three determinations ± SE from bone marrow cells pooled from the femurs of two mice.

Fig. 3. The effect of multiple i.p. injections or chronic oral dosing of BSO on mouse tissue GSH levels. Injections of BSO (MIP) were given every 6 h x 5 (450 mg/kg). BSO was given orally (p.o.) in the animals' drinking water (20 HIM) for 3 days following a single i.p. injection of a loading dose of BSO (450 mg/kg). GSH concentrations were determined either 6 h after the last injection of BSO, or 6 h after withdrawal of BSO from the animal's drinking water. Each value is the mean ± SE of determinations on five animals.

Fig. 4. The effect of multiple injections of BSO on bone marrow and L-PAM-resistant murine L1210 leukemia GSH concentrations. BSO was administered every 6 h x 5 (450 mg/kg; i.p.) and cells were harvested and GSH levels determined as described in the legend to Fig. 2. Values are the mean ± SE of determinations on five tumored animals, and as three determinations on bone marrow samples pooled from the femurs of six nontumor bearing animals. * significantly different from control values (P < 0.01).

Fig. 5. The effect of chronic oral (p.o.) or multiple injection (MIP) of BSO on the toxicity of L-PAM in BDF mice. BSO was administered as described in the legend to Fig. 3. L-PAM was administered either 6 h after the withdrawal of BSO from the animals' drinking water or 6 h after the last injection of BSO. Lethality at 7 days was determined on groups of six animals.

decreased by more than 90% to levels that were comparable to those found in marrow cells (Fig. 4). In contrast, the concentration of GSH in bone marrow was decreased only by 40%, making this the most resistant tissue to thiol depletion by BSO.

Toxicity. The degree of thiol depletion produced by these two dosing regimens translated into different susceptibilities to the toxicity resulting from the administration of L-PAM (Fig. 5). The dosing regimen which maximally depleted GSH (MIP) produced a marked shift of the lethality curve, resulting in a 1.6-fold reduction in the LD50 for L-PAM. Oral dosing of BSO increased lethality only at high doses, resulting in a decrease in the LD50 for L-PAM. The actual cause of death in these animals is not known. However, L-PAM was myelosuppressive as shown by the dose-dependent decrease in peripheral WBC counts (Fig. 6). BSO was found to have little effect on the myelosuppressive activity of L-PAM at the time of the WBC nadir, on day 4. However, BSO markedly inhibited the recovery of the WBC population that was observed on day 8 in animals that received only L-PAM. BSO alone was not found to be toxic by the.
indices of toxicity reported in this study (i.e., lethality or WBC counts). Chronic BSO administration did result in a slight loss of weight that recovered rapidly after cessation of treatment (not shown). As in the previous experiments, l-PAM was administered 6 h after the last dose of BSO to minimize possible drug-drug interactions.

In Vivo Sensitization of L1210<sub>R</sub> to l-PAM by BSO. Pretreatment of animals with MIP injections of BSO prior to l-PAM administration was not found to have an appreciable effect on the antitumor activity of l-PAM as judged by median survival times (Table 1). The slight increase in life-span produced by BSO pretreatment (i.e., 10% relative to treatment with 10 mg/kg l-PAM alone) was equivalent to a log-fold increase in tumor kill as determined by the survival curve generated by plotting median survival <i>versus</i> the number of inoculated L1210<sub>R</sub> cells (not shown). However, BSO was found to increase toxicity at the highest tested dose of l-PAM (i.e., 13 mg/kg), shown by the reduction in mean survival (Table 1). The relative lack of effect that BSO pretreatment had on the antitumor activity of l-PAM occurred in spite of the fact that tumor GSH levels were decreased by more than 90% at the time of the L-PAM injection (Fig. 4). This observation prompted additional studies on the possible sensitization of l-PAM by BSO.

In this regard, MIP injections of BSO increased the cytotoxicity of l-PAM as shown by the decreased cloning efficiency of L1210<sub>R</sub> cells harvested from animals treated <i’in vivo</i> with BSO and/or l-PAM (Table 2). BSO treatment alone produced a slight reduction (i.e., 10%) in cloning efficiency. BSO in combination with l-PAM (2.5 mg/kg) decreased the clonogenicity of L1210<sub>R</sub> cells by 92% compared to the 78% decrease produced by treatment with l-PAM alone. Moreover, the recovery of tumor cells from the peritoneum of l-PAM-treated animals was far less than in control animals, and BSO pretreatment resulted in an even further decrease in tumor cell recovery (Table 2). This observation suggested that a considerable degree of toxicity and cell death, may have occurred in the 18 h that had elapsed from the time of the L-PAM injection to the harvesting of the tumor cells for the clonogenic assay. In order to investigate the early effect of BSO/L-PAM treatment and to minimize the procedural artifacts that occur in the multiple manipulations required to perform such <i’in vivo/in vitro</i> experiments, an <i’in vivo</i> labeling assay was adopted.

[<sup>[3]H</sup>TdR] incorporation into L1210<sub>R</sub> cells was increased 3 h after administering a low dose of l-PAM (i.e., 0.5 mg/kg; Fig. 7). At higher doses, l-PAM produced a dose-dependent decrease in DNA synthesis as shown by the decrease in [<sup>[3]H</sup>TdR] incorporation. BSO pretreatment inhibited both the increase in [<sup>[3]H</sup>TdR] incorporation that occurred at low dose l-PAM, and at higher doses of l-PAM, caused a further reduction in DNA synthesis compared to treatment with l-PAM alone. The ED<sub>50</sub> of l-PAM for inhibition of [<sup>[3]H</sup>TdR] incorporation was esti-

**Table 2 Effect of buthionine sulfoximine pretreatment on the antitumor activity of L-PAM in vivo on the clonogenicity of L-PAM-resistant murine L1210 leukemia cells in vitro**

<table>
<thead>
<tr>
<th>L-PAM dose (mg/kg)</th>
<th>BSO&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Cloning efficiency&lt;sup&gt;b&lt;/sup&gt; (% of control)</th>
<th>Total cells/mouse (x 10&lt;sup&gt;5&lt;/sup&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
<td>100 ± 0&lt;sup&gt;4&lt;/sup&gt;</td>
<td>5.6 ± 2.9</td>
</tr>
<tr>
<td>0.5</td>
<td>+</td>
<td>90 ± 2&lt;sup&gt;4&lt;/sup&gt;</td>
<td>4.7 ± 3.2</td>
</tr>
<tr>
<td>1</td>
<td>None</td>
<td>71 ± 2&lt;sup&gt;4&lt;/sup&gt;</td>
<td>2.2 ± 1.7&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>2.5</td>
<td>None</td>
<td>60 ± 3&lt;sup&gt;2&lt;/sup&gt;</td>
<td>1.9 ± 1.2&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>2.5</td>
<td>+</td>
<td>22 ± 15&lt;sup&gt;4&lt;/sup&gt;</td>
<td>1.4 ± 1.6&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>2.5</td>
<td>+</td>
<td>8 ± 6&lt;sup&gt;4&lt;/sup&gt;</td>
<td>0.1 ± 0.06&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Administered as multiple i.p. injections (450 mg/kg every 6 h x 5) starting 5 days after tumor inoculation (1 x 10<sup>6</sup> L-PAM-resistant murine L1210 leukemia cells); L-PAM was administered as a single i.p. injection 6 h after the last dose of BSO or 6 days after tumor inoculation and tumor cells were harvested 18 h after l-PAM administration as described in "Materials and Methods."

<sup>b</sup> Cloning efficiency was assessed by clonal growth of surviving cells in soft-nutrient agar and is expressed as percentage of control (6).

<sup>c</sup> Mean ± SD of triplicate cultures from three animals.

<sup>d</sup> Statistically different from control; <i>P</i> > 0.05.

<sup>e</sup> Statistically different from animals receiving the same dose of l-PAM, but no BSO; <i>P</i> < 0.05.

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Fig. 6. The effect of BSO pretreatment on l-PAM-induced alterations in peripheral WBC counts. L-PAM was administered 6 h after the last injection of BSO (0, 450 mg/kg every 6 h x 5) or saline vehicle (O), and WBC counts were determined on day 4 (solid lines) or day 5 (hashed lines) after l-PAM treatment. Values are expressed as percentage of control and are the mean ± SE of determination from five animals.

Table 1 Effect of buthionine sulfoximine pretreatment on the antitumor activity of L-PAM

<table>
<thead>
<tr>
<th>L-PAM dose (mg/kg)</th>
<th>BSO&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Median survival (days)</th>
<th>T/C (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>T/C (%)&lt;sup&gt;b&lt;/sup&gt; + (L-PAM)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
<td>11.2 ± 0.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>100 ± 4</td>
<td>100 ± 4</td>
</tr>
<tr>
<td>0</td>
<td>+</td>
<td>10.2 ± 0.4</td>
<td>91 ± 4</td>
<td>91 ± 4</td>
</tr>
<tr>
<td>10</td>
<td>None</td>
<td>13.4 ± 1.2</td>
<td>120 ± 11</td>
<td>120 ± 11</td>
</tr>
<tr>
<td>10</td>
<td>+</td>
<td>14.8 ± 0.7</td>
<td>132 ± 6</td>
<td>110 ± 5</td>
</tr>
<tr>
<td>13</td>
<td>None</td>
<td>14.8 ± 2.3</td>
<td>132 ± 20</td>
<td>132 ± 20</td>
</tr>
<tr>
<td>13</td>
<td>+</td>
<td>9.8 ± 2.2</td>
<td>88 ± 19</td>
<td>66 ± 15</td>
</tr>
</tbody>
</table>

<sup>a</sup> Administered as multiple i.p. injections (450 mg/kg every 6 h x 5) starting 18 h after tumor inoculation (1 x 10<sup>6</sup> L-PAM-resistant murine leukemia L1210 cells); L-PAM was administered as a single i.p. injection 6 h after the last BSO dose and 48 h after tumor inoculation.

<sup>b</sup> Median day survival in treated animals was expressed as a percentage of the median day survival of animals that had received no treatment (i.e., 11.2 ± 0.6).

<sup>c</sup> The median day survival in BSO-treated animals was expressed as a percent of the median day survival of animals that had received only l-PAM.

<sup>d</sup> Mean ± SD; <i>N</i> = 6.

Fig. 7. The effect of BSO pretreatment on the incorporation of [<sup>[3]H</sup>]thymidine into L-PAM-resistant L1210 cells <i’in vivo</i>. [<sup>[3]H</sup>]TdR was administered by i.p. injection (1 uCi/g) 3 h after the administration of L-PAM to BSO- or saline-pretreated mice as described in the legend to Fig. 6. Tumor cells were harvested 1 h after [<sup>[3]H</sup>]TdR administration and values are expressed as the mean ± SE on determinations from four animals.
CHEMOSENSITIZATION OF L-PAM BY BSO

The results of the present study indicate that BSO effectively reduced GSH concentrations in normal and in tumor tissue without producing appreciable toxicity. BSO was, however, found to potentiate both the toxicity and antitumor activity of L-PAM. The increase in L-PAM toxicity depended upon the degree of thiol depletion (Fig. 5) and was observed only at much higher doses of L-PAM (Figs. 5 and 6) than required to produce an increase in antitumor activity (Table 2 and Fig. 7). Using decreased thymidine incorporation to estimate the antitumor activity of L-PAM, BSO was found to increase the therapeutic index (LD10/ED50) of L-PAM from 3.6 to 6.5. These results in vivo support in vitro studies which have shown that GSH depletion increased tumor sensitivity to a number of antineoplastic agents (6–8, 15–17). However, the present findings provide the first indication that tumor tissue may be more sensitive than normal tissue to L-PAM toxicity following GSH depletion by BSO, and suggests that thiol modulation by BSO may be useful as an adjuvant in cancer chemotherapy.

The observation that some tissues (e.g., bone marrow) were comparatively resistant to GSH depletion by BSO, whereas other tissues (e.g., kidney) were particularly sensitive to BSO, may provide a basis for the rational selection of drugs which can be used in combination with BSO. For example, recent studies have shown that BSO pretreatment markedly increased the renal toxicity of MeCCNU (18) and cis-platinum (25), two agents with a predisposition towards nephrotoxicity. In contrast, the bone marrow was found to tolerate, reasonably well, the combination of BSO and therapeutic doses of L-PAM (Fig. 6). It is possible that combination therapies involving anticancer agents that are predominantly myelosuppressive may be better tolerated than agents that are reported to cause renal, hepatic, or cardiac toxicities. This observation does not preclude the need to monitor the degree of myelosuppression, or other toxicities, that may result from combination therapies involving thiol depletion.

In the present study, BSO was found to be somewhat effective at sensitizing the L1210R tumor cells found within the peritoneal cavity to L-PAM (Table 2; Fig. 7). However, BSO failed to cause a significant increase in the life-span of tumor-bearing animals (Table 1) despite a 90% reduction in tumor GSH concentrations (Fig. 5). This observation is not surprising in light of the well-known metastatic potential of the murine L1210 leukemia. The failure to observe a greater increase in the life-span of these animals probably was due to metastatic infiltration into specific host organs, notably the liver. Recent studies have shown that hepatic metastasis arising from i.p. inoculation of L1210 cells had elevated GSH levels and were more resistant to L-PAM compared to their counterparts found in the peritoneal cavity (26). Pharmacokinetic differences between the metastatic and primary tumor not withstanding, such differences in GSH metabolism may provide an explanation for the ineffectiveness of BSO at prolonging life-span, and highlights the potential importance of GSH as a determinant in drug resistance. In contrast to the present findings in the murine L1210 leukemia, recent studies with a human ovarian carcinoma cell line have shown that BSO significantly prolonged survival in L-PAM-treated nude mice (27).

It is clear that GSH plays an important role in the cellular protection against a variety of antineoplastic agents. However, the potential usefulness of BSO or other thiol-modulating drugs is limited not only by a thorough understanding of possible drug interactions and/or host toxicities that may arise from combination therapies with various antineoplastic drugs, but also by an understanding of GSH metabolism by the tumor systems in which these therapies may be used.

REFERENCES

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