Dose Escalation of the Hypoxic Cell Sensitizer Etanidazole Combined with Ifosfamide, Carboplatin, Etoposide, and Autologous Hematopoietic Stem Cell Support


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ABSTRACT

Multiple mechanisms of drug resistance contribute to treatment failure. Although high-dose therapy attempts to overwhelm these defenses pharmacologically, this approach is only successful in a fraction of treated patients. Many drug resistance mechanisms are shared between malignant and normal cells, but the expression of various drug resistance mechanisms associated with hypoxia is largely confined to tumor tissue. Thus, reversal of this mechanism is likely to provide a therapeutic advantage to the host. This study was designed to define the dose-limiting toxicities and maximum tolerated dose of etanidazole when it is given concurrently with high-dose ifosfamide, carboplatin, and etoposide (ICE), with hematopoietic stem cell support. The maximum tolerated doses of high-dose ICE were administered concurrently with dose escalations of etanidazole, a hypoxic cell sensitizer. All agents were given by 96-h continuous i.v. infusion beginning on day −7. Mesna uroprotection was provided. Autologous marrow and cytokine mobilized peripheral blood progenitor cells were reinfused on day 0. Granulocyte colony-stimulating factor was administered following reinfusion until the granulocytes recovered to >1000/μL. Fifty-five adults with advanced malignancies were enrolled in cohorts of five to nine patients. Four dose levels of etanidazole between 3 and 5.5 g/m²/day (12, 16, 20, and 22 g/m² total doses) and two doses of carboplatin (1600 and 1800 mg/m² total doses) were evaluated. Seven patients died of organ toxicity (13%); two each from veno-occlusive disease of liver and sepsis; and one each from sudden death, renal failure, and refractory thrombocytopenic hemorrhage. Five deaths occurred at the top dose level. One additional patient suffered a witnessed cardiorespiratory arrest from ventricular fibrillation and was resuscitated. Dose-dependent and largely reversible peripheral neuropathy was observed consisting of two syndromes: severe cramping myalgic/neuropathic pain, predominantly in stocking glove distribution, occurring between day −3 and day 0, and a sensory peripheral neuropathy with similar distribution peaking around day +60. The maximal achievable dose of etanidazole (16 g/m² dose level) resulted in a mean serum level of 38 μg/mL (25–55 μg/mL). Etanidazole significantly enhanced host toxicity of high-dose ICE. Effective modulatory doses of etanidazole could not be given with acceptable toxicity using this schedule.

INTRODUCTION

Multiple mechanisms of drug resistance contribute to treatment failure. Although high-dose therapy attempts to overwhelm these defenses pharmacologically, this approach is only successful in a fraction of patients treated. Many drug resistance mechanisms, such as membrane transport, thiol scavenging, and DNA repair, are shared between malignant and normal cells. Mechanisms of resistance to chemotherapy and radiotherapy that are associated with tissue hypoxia include prolongation of the cell cycle and low concentrations of oxygen and peroxide radicals, which, under oxic conditions, stabilize reactive free radicals for a longer duration of action, resulting in increased DNA damage (1–4). Although most host tissues are well oxygenated under normal circumstances, even microscopic tumors contain significant cell populations that are profoundly hypoxic. Thus, reversal of this major multidrug resistance mechanism, largely confined to tumor tissue, is likely to provide a therapeutic advantage to the host.

Nitroimidazole compounds have the properties of hypoxic cell radiosensitizers, which diffuse into hypoxic tissues and restore their sensitivity to radiation without augmenting radiation effects in normally oxygenated tissues. They also demonstrate chemosensitization to various alkylating agents (5). In addition to behaving as oxygen mimics, the nitroimidazoles appear to have modest direct cytotoxicity in an hypoxic environment, probably mediated by reactive intermediates, such as the nitro-radical anion (6). Increased DNA cross-linking of alkylating agents has been observed (7–10). Other mechanisms have also been invoked, including depletion of intracellular glutathione (11) and, with mitomycin, decreased clearance of certain alkylating agents at high doses (12), perhaps caused by
inhibition of P450 metabolism (13). This latter effect has not been previously observed with etanidazole (14). The efficacy of each drug in the ICE \(^1\) regimen is reduced under conditions of hypoxia. In preclinical models, these drugs demonstrate significantly enhanced cytotoxicity when combined with etanidazole, oxygen with oxygen carriers, or other modulators of hypoxia (14–20). The dose-modifying effects of etanidazole are greater at higher chemotherapy doses, providing a strong rationale to test these modulators at transplant doses.

This study was designed to define the DLTs and MTD of etanidazole when it is given concurrently with high-dose ICE, with hematopoietic stem cell support. We have previously reported a Phase I dose escalation study of the combination of ICE with autologous hematopoietic support (21). A 96-h continuous infusion schedule was chosen to maximize potential synergism (22, 23) and to potentially reduce end-organ toxicity (24).

**PATIENTS AND METHODS**

**Eligibility.** Eligible adults (ages 18–59 years) had histologically documented malignancies without major comorbid disease, performance status scores of 0–1, WBC counts of \( \geq 3000/\mu L \), platelet counts of \( \geq 100,000/\mu L \), creatinine and bilirubin levels of \( \leq 1.5 \) times normal levels, creatinine clearance of \( \geq 60 \) mL/min, and aspartate aminotransferase levels of \( \leq 2.5 \) times normal levels. Patients with extensive-stage small cell carcinoma, stage IIIIB non-SCLC, and metastatic sarcoma were eligible if they were responding to standard dose regimens; other patients had failed first-line conventional regimens. Patients with bone marrow or central nervous system metastases were excluded. The study was approved by the institutional review boards of the Beth Israel Hospital, the Dana-Farber Cancer Institute, and the Dartmouth-Hitchcock Cancer Center. Written informed consent was required.

**Chemotherapy.** Etanidazole was supplied by the National Cancer Institute (Bethesda, MD). Chemotherapeutic agents were given by 96-h continuous i.v. infusion (days −7 to −3; Ref. 21). Mesna was continued for an additional 24 h. Five percent dextrose with sodium bicarbonate (44–88 meq/liter) at 200 mL/h was given to prevent ifosfamide- or etoposide-associated metabolic acidosis. Barbiturates and steroids were avoided due to potential alteration of ifosfamide metabolism by P450 induction.

Total doses of ifosfamide and etoposide were fixed at 16 and 1.2 g/m², respectively. Carboplatin was initially given at 1.6 g/m² and then escalated to 1.8 g/m² (the MTD of ICE) to evaluate possible additive neuropathy from etanidazole and carboplatin. Etanidazole was begun at 12 g/m² over 96-h continuous infusion and escalated by 0.25–0.5 mg/m²/day across dose levels. Three to five patients were initially entered on a particular dose level. Doses were escalated if fewer than two of these patients had DLT over a 28-day observation period. Additional patients were allowed on study without dose escalation during

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\(^1\) The abbreviations used are: ICE, ifosfamide, carboplatin, and etoposide; DLT, dose-limiting toxicity; MTD, maximum tolerated dose; SCLC, small cell lung cancer; eq. equivalent; PBPC, peripheral blood progenitor cell; CSF, colony-stimulating factor; CI, confidence interval; VOD, veno-occlusive disease.

**RESULTS**

**Patient Characteristics.** Between March 1992 and March 1994, 59 adults with advanced malignancies (median age = 41 years; range, 19–58 years) were enrolled into the study protocol at six dose levels. The median number of prior chemotherapy regimens was two (range, one to four). All patients had prior exposure to at least one of the agents in the ICE
regimen. Histopathological diagnoses included advanced sarcoma (18), relapsed or refractory germ cell carcinoma (14), ovarian carcinoma (9), and small cell carcinoma (8). Of these 59 patients, 27 were in first response, and 7 were refractory to conventional chemotherapy (Tables 1 and 2).

**Toxicity.** Four dose levels of etanidazole between 3 and 5.5 g/m²/day (12, 16, 20, and 22 g/m² total doses) and two doses of carboplatin (1600 and 1800 mg/m² total doses) were evaluated (Table 3). Also presented are the toxicity profiles of 25 patients treated with the same two dose levels of ICE without etanidazole as part of the immediately preceding clinical trial (21). ICE alone is associated with renal, mucosal, and occasional central nervous system toxicity. However, etanidazole significantly enhanced certain host toxicities of ICE. These toxicities are reviewed by organ system below.

VOD (13%) at an etanidazole dose of 22 g/m² was dose limiting. Seven patients died of organ toxicity (13%); two each from VOD of liver and sepsis and one each from sudden death, renal failure, and refractory thrombocytopenic hemorrhage. Five deaths occurred at the top dose level (see “Patients and Methods”). One additional patient suffered a witnessed cardiopulmonary arrest from ventricular fibrillation and was resuscitated. One of the two cardiac arrests was associated with a possible platelet transfusion reaction (20 g/m² dose level), and the other was associated with intermittent hypokalemia as low as 2.8 mg/dl (16 g/m² level).

The steady-state serum level of etanidazole correlated directly with the dose level of etanidazole, although toxicities associated more tightly with dose level. The maximal achievable dose of etanidazole (16 g/m² dose level) resulted in a mean serum level of 38.49 μg/ml (25.31–54.93 μg/ml).

**Neurotoxicity (Peripheral).** Characteristic cramping myalgia/neuralgia, described previously with etanidazole and concurrent radiotherapy, occurred in a dose-dependent fashion at dose levels of 16 g/m² and above (P = 0.03 for grade 3 toxicity or higher). The painful neuralgia developed after 72–96 h of etanidazole infusion in a stocking glove distribution, requiring morphine for relief, and resolved by 48–72 h after completion of the drug. With the use of etanidazole, late development of peripheral sensory neuropathy (1 of 25 versus 18 of 59; P = 0.008) or otoxicity (3 of 25 versus 12 of 59; P = 0.36) was more common, particularly for those patients with preexisting cisplatin-induced neuropathy (5 of 15 versus 12 of 17; P = 0.04). In these situations, the neuropathy developed by 2 months posttransplant and gradually lessened over the next 6–12 months.

**Neurotoxicity (Central).** Somnolence and occasional hallucinations or confusion were observed in 16 (27%) patients, beginning on day 3 or 4 of chemotherapy. In most patients, these symptoms resolved within 1 week. This toxicity was not significantly greater in the presence of etanidazole (4 of 25 versus 16 of 59; P = 0.27). Despite being reversible, the syndrome and developing mucositis contributes greatly to aspiration pneumonia risk.

**Genitourinary Toxicity.** Thirty-three (56%) of 59 patients developed non-oliguric creatinine elevations (range, 1.5–9.3 mg/dl). Of these, eight developed creatinine elevations of >3 mg/dl. All minor and most grade 3 creatinine elevations resolved. No patients received dialysis. The rise in serum creatinine usually began by the end of the 96-h infusion (day −3) and peaked 48–72 h later. Renal toxicity was not clearly increased by etanidazole (11 of 25 versus 33 of 59; P = 0.32). The early stopping rule was invoked in 4 of 59 patients (7%). With chemotherapy halted, the resulting renal toxicity was mild in three patients (peak creatinine levels of 1.9, 2.5, and 2.9 mg/dl) and fully reversible, but the fourth patient died with hypotensive culture negative shock, bleeding, and multiorgan failure (peak creatinine level, 7.2 mg/dl).

Transient renal wasting of electrolytes and glucose, compatible with a non-anion gap proximal renal tubular acidosis, was universally seen. The serum bicarbonate (HCO₃⁻) level dropped below 20 meq/liter in all but eight patients, despite administration of 10–20 meq of NaHCO₃ during the first week of therapy. Vigorous replacement of potassium, calcium, magnesium, and phosphate was required in all patients. Grades 2 and 4 hematuria were observed once each.

**Gastrointestinal Toxicity.** Severe mucositis, manifested by either odynophagia and esophageal spasm or oral mucositis, was observed in 35 (59%) patients. No relationship with etanidazole dose was observed (14 of 25 versus 35 of 59; P = 1.00). Of these patients, mean duration of any mucositis was 12 days (range, 6–20 days). Nausea and vomiting was generally adequately controlled with antiemetics. Diarrhea was common, transient, and mild to moderate in all but one case. Iatrogenic hyperglycemia was frequently seen, but with no clinical consequence.

Reversible elevations in aspartate aminotransferase, within a week of completing chemotherapy, were observed in 24% of patients. Elevations in bilirubin were also seen 2–3 weeks after completion of chemotherapy in 68% of patients and were more common with the use of etanidazole (3 of 25 versus 40 of 59; P < 0.0001). Except for the two patients who died of VOD, all other bilirubin elevations resolved completely without stigmata of VOD.

**Cardiorespiratory Toxicity.** One patient died of sudden death shortly after receiving a platelet transfusion. This patient had recovered from grade 4 pulmonary toxicity consisting of capillary leak syndrome requiring oxygen. A second patient developed ventricular fibrillation but recovered completely after successful resuscitation. No cardiac irritability had been observed in either case before the event. Six patients developed supraventricular tachycardia that did not require treatment, and there was an episode of atrial fibrillation/flutter that resolved with medical management.

Seven patients developed severe dyspnea at rest that was associated with fluid buildup in the lungs and pleural spaces.

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**Table 1** Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number entered</td>
<td>59</td>
</tr>
<tr>
<td>No. of males/no. of females</td>
<td>33/26</td>
</tr>
<tr>
<td>Performance status (% of patients)</td>
<td>0 48% 1 52%</td>
</tr>
<tr>
<td>Median age, yr (range)</td>
<td>41 (19–58)</td>
</tr>
<tr>
<td>Median no. of prior regimens (range)</td>
<td>2 (1–4)</td>
</tr>
<tr>
<td>Median no. of prior cycles (range)</td>
<td>7 (3–21)</td>
</tr>
<tr>
<td>Median no. of prior drugs (range)</td>
<td>5 (2–12)</td>
</tr>
</tbody>
</table>

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Dyspnea was associated with multiorgan failure in four patients, capillary leak in two patients, and candidal pneumonitis associated with progressive SCLC in one patient.

**Hematological Toxicity.** Absolute neutropenia (granulocyte counts of <500/μl) and thrombocytopenia (platelet counts of <20,000/μl) were observed for a median of 13 (range, 8–49) and 17 (range, 4–52) days, respectively, and were unaffected by dose level. Four episodes of bacteremia and 10 line infections were documented.

**Response and Survival.** Twenty-three of 59 patients were not evaluable for response (disease not measurable or evaluable for response in 17 and toxic deaths in 6; Table 4). Nine (25%) and 13 (36%) evaluable patients achieved complete and partial responses, respectively, for an overall response rate of 61%. Five patients with germ cell carcinoma remain disease free (>55 and >51 months), two with alveolar rhabdomyosarcoma (>55 and >51 months), two with diffuse undifferentiated non-Burkitt’s lymphoma (>36 and >39 months), and one each with...
extrapulmonary small cell carcinoma (>44 months) and peripheral neuroectodermal tumor (>33 months). With a median follow-up of 31 months (range, 9–51 months), the median event-free and overall survivals are 7 months (0.3–51 months) and 27 months (range, 0.3–51 months), respectively (Fig. 1).

**DISCUSSION**

The principal objectives of this study were to define the DLTs and the MTDs of the hypoxic cell sensitizer etanidazole when given concurrently with a 96-h continuous infusion of high-dose ICE with autologous stem cell support. The rationale for this study is provided by the observed broad-spectrum antitumor activity of ICE at conventional doses in SCLC, non-SCLC, germ cell carcinoma, ovarian cancer, and lymphomas and, therefore, potential broad applicability. This combination of chemotherapeutic agents demonstrates enhanced cytotoxicity when combined with etanidazole under hypoxic conditions (14–20). Preclinical modeling suggested that the modulating effects and the therapeutic ratio between normal and malignant tissues may actually increase with dose escalation of certain alkylating agents (16).

An ideal modulator of drug resistance would circumvent or reverse a commonly observed cause of pan-drug resistance restricted in expression to tumor tissue. Hypoxia does represent a cause of broad drug resistance restricted primarily to tumor tissue because host tissues are euoxic at rest with the exception of low oxygen partial pressures in normal cartilage. The modulator should not require compromise of chemotherapeutic drug dose due to enhancement of host toxicity.

Etanidazole, a low molecular weight highly lipid-soluble compound, is rapidly and widely distributed in all tissues with essentially equivalent serum and tissue levels (32). Unlike oxygen-carrying agents, etanidazole does not reverse hypoxia itself. Serum levels of >70–100 μg/ml are associated with effective modulation of hypoxic tumor cell drug resistance in animal models (32). With the exception of dose rate and cumulative dose-limiting peripheral sensory neuropathy, other host toxicities of etanidazole are infrequent (25, 33–35). Sustained drug level and/or duration of exposure may be more important than peak level, providing the rationale for a continuous infusion administration (36). Pharmacological modeling of etanidazole has been tested extensively (25) and assumes stability in the elimination constant (i.e., the renal glomerular filtration rate).

The observed dose-dependent painful cramping neuralgia and increased peripheral sensory neuropathy are consistent with experience with etanidazole as a single agent combined with radiotherapy or with conventional dose chemotherapy, although carboplatin may have contributed to its severity. Continuous infusion etanidazole over 96 h has been evaluated in conjunction with brachytherapy (36). The maximum dose delivered was 23 g/m² over 96 h, which produced a steady-state serum concentration of 50–132 μg/ml. Seven of 18 patients treated at 20–23 g/m² developed arthralgias, tingling, or abdominal cramping, necessitating early cessation of the infusion in 4 patients. Although these symptoms generally resolved completely within a few hours to a few weeks following treatment, they were considered dose limiting.

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**Table 4 Response by histology**

<table>
<thead>
<tr>
<th>Tumor</th>
<th>No. of patients</th>
<th>No. of responses</th>
<th>% overall response</th>
<th>Progression-free for ≥2 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarcoma&lt;sup&gt;a&lt;/sup&gt;</td>
<td>18</td>
<td>12</td>
<td>50</td>
<td>3</td>
</tr>
<tr>
<td>Testis</td>
<td>14</td>
<td>10</td>
<td>60</td>
<td>5</td>
</tr>
<tr>
<td>Ovary</td>
<td>9</td>
<td>5</td>
<td>80</td>
<td>0</td>
</tr>
<tr>
<td>SCLC/EPSC</td>
<td>8</td>
<td>3</td>
<td>33</td>
<td>1</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>6</td>
<td>5</td>
<td>80</td>
<td>2</td>
</tr>
<tr>
<td>Others&lt;sup&gt;d&lt;/sup&gt;</td>
<td>4</td>
<td>1</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>59</td>
<td>36</td>
<td>61</td>
<td>11 (19%)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Median event-free survival = 7 months (range, 0.3–51 months). NMD, disease not measurable or evaluable for response; ED, early death; CR, complete response; PR, partial response; EPSC: extrapulmonary small cell carcinoma.

<sup>b</sup> Evaluable patients only.

<sup>c</sup> Sarcomas: three rhabdomyosarcomas, six leiomyosarcomas, two peripheral neuroectodermal tumors, two angiosarcomas, and one each of mesothelioma, endometrial stromal cell sarcoma, osteosarcoma, fibrosarcoma, and desmoplastic round cell sarcoma.

<sup>d</sup> Other: two breast cancers and one each of head and neck and non-small cell lung cancer.
High-dose ICE with etanidazole was associated with significantly worse hepatic and, possibly, cardiac toxicity than that encountered in the prior study using high-dose ICE alone when controlling for dose (Tables 1 and 2). The dose-limiting liver toxicity, in the form of hyperbilirubinemia and VOD were the most serious toxicities associated with the combination of high-dose ICE and etanidazole. This toxicity has not been observed in 42 patients receiving these dose levels of high-dose ICE alone (Ref. 21; 0 of 42 versus 2 of 18; P = 0.03).4 Moreover, 5 of 18 patients ultimately died of toxicity at this dose level.

Another DLT was sudden death, which occurred in one patient at this dose level. Ventricular fibrillation occurred in another patient at the 16 g/m² dose level. This patient remains free from progression and clinically free of cardiac disease 2.5 years later. The occurrence of these two events decreases the assurance that a MTD of etanidazole can be identified in this context. The significant electrolyte fluxes that occur universally with ifosfamide or amphotericin administration due to the associated renal tubular dysfunction may also have contributed to arrhythmia susceptibility.

The frequency and severity of renal and mucosal toxicity appeared to be similar in the presence or absence of etanidazole. Severe renal toxicity appeared to be more common at this dose level but was observed in the setting of late multiorgan failure rather than early in the transplant course, as would be seen with ifosfamide-associated toxicity.

ICE alone is certainly capable of producing these severe toxicities (with exception of the cramping neuralgia; Ref. 37). However, with the dose schedule of ICE used in this trial, etanidazole seems to have increased these visceral toxicities over that expected for ICE alone (21, 38). Specific effects of etanidazole, independent of its hypoxic cell sensitization documented in preclinical studies, might potentially explain these enhanced toxicities. Hepatic glutathione depletion during etanidazole administration has been described (39) and could predispose to VOD, particularly when given concurrently with alkylating agents. Etanidazole has been described as causing lipid peroxidation of cellular membranes (40). This could lead to endothelial cell membrane damage, perhaps contributing to both VOD and arrhythmia susceptibility. Although no increase in normal tissue toxicity has been observed when combining etanidazole with conventional dose chemotherapy (41, 42), high-dose alkylating agents may place sufficient stress on the normal host protective elements to tip the balance. We are also exploring whether etanidazole may have altered the pharmacological parameters of the high-dose alkylating agents, i.e., increased drug exposure.5

These mechanisms are presumably independent of hypoxic cell sensitization. Because the DLTs encountered are observed with many other transplant regimens in the absence of etanida-

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