Synergistic Antitumor Activity of Cisplatin and Interleukin 1 in Sensitive and Resistant Solid Tumors

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ABSTRACT

The antitumor activity of cis-diaminedichloroplatinum(II) (cP) and human recombinant interleukin-1α (IL-1α) was studied in RIF-1 and SCC VII solid tumor models and in a cP-resistant subline of RIF-1 designated RIF-R1,p. In RIF-1 tumors, clonogenic cell survival after cP plus IL-1α combinations was highly schedule and IL-1α dose dependent. More than additive clonogenic cell kill was seen when cP was given 6 h before, but not 8 h before or at 2–6 h after IL-1α. Time course studies indicated that maximal clonogenic cell killing was achieved within 4–6 h after the cP plus IL-1α combination, with little or no recovery for up to 24 h. In vivo dose-response studies indicated that cP plus IL-1α combinations induced more clonogenic cell kill than cP alone in all three tumor models, and analysis by the median effect principle indicated highly synergistic antitumor activity. Dexamethasone but not indomethacin inhibited the synergistic interaction. IL-1α had no effect on the cytotoxicity of cP in SCC VII cells in vitro, and neither in vitro hypoxia nor in vivo ischemia, induced by clamping tumor blood supply, significantly affected cP clonogenic cell killing. Increased clonogenic cell killing was seen, however, after removal of the clamp, implicating reperfusion events, such as oxyradical stress, as a potential mechanism for increased cP cytotoxicity in SCC VII solid tumors. The data from our model systems provide a rationale for additional work to define the mechanisms of the synergistic antitumor activity of the cP plus IL-1α combination and indicate that IL-1α might be a useful adjunct to increase the clinical efficacy of cP-containing strategies for both sensitive and cP-resistant cancers.

INTRODUCTION

Interleukin 1 is a distal mediator of immune and inflammatory responses. In addition to immune cells, this pleiotropic cytokine is produced by many other cells including fibroblasts (1, 2), keratinocytes (3–6), squamous tumor cells (7, 8), glial cells (9), and endothelial cells (10, 11). These cells can also be targets for IL-1-stimulated activities (11–13). Although IL-1 was reported to be cytostatic in some melanoma (14), ovarian carcinoma (15), osteogenic sarcoma (16), and MCF-7 breast cancer (17) cell lines, little or no effect was seen on the clonal growth of primary human tumor explant cultures (18). In vivo, IL-1α can have growth-inhibitory activity in highly immunogenic tumors, but little clonogenic cell kill or tumor growth inhibition is seen in nonimmunogenic or weakly immunogenic solid tumors (19, 20). Marked pathophysiological perturbations including reduced tumor perfusion, reduced high-energy phosphate reserves, microvascular injuries, and acute hemorrhagic necrosis were, however, observed within 4 h after administration of the cytokine to mice bearing nonimmunogenic tumors (19–21). Tumor hypoxia is a likely consequence of IL-1α treatment, since agents known to be preferentially cytotoxic to hypoxic cells exhibited schedule-dependent supraadditive cytotoxicity in combination with IL-1α (22, 23).

In preliminary studies (24, 25) we noted that IL-1α and cP might also produce more than additive clonogenic cell kill. Since cP is not thought to be preferentially cytotoxic to hypoxic cells (26), the possibility that other mechanisms could account for these observations has prompted new detailed studies to define schedule, time, and dose-response relationships for IL-1α and cP in sensitive (RIF-1, SCC VII) and cP-resistant (RIF-R1,p) models. Our results indicate that clonogenic cell kill by IL-1α plus cP combinations is consistent with synergistic interactions in vivo. These activities can be inhibited by dexamethasone but not by indomethacin. Furthermore, the results indicated that ischemia per se has little or no effect on in vivo cP cytotoxicity.

MATERIALS AND METHODS

Tumor Models. The RIF-1 and SCC VII murine tumor models were propagated in vitro and in vivo as described previously (19, 20, 22). The RIF-1 cell clone was isolated from RIF-1 cells by selection for growth in cP (0.3 μg/ml) media. RIF-1,p cells are approximately 8-fold more resistant to cP in vitro compared to the RIF-1 parent line. These cells are resistant to CdCl₂ but not H₂O₂, and they form fibrosarcomas when implanted in C3H/HeJ mice. All cell lines were grown in vitro in RPMI 1640 supplemented with 15% newborn bovine serum, 2 mg/ml glutamine, and 1 μg/ml gentamicin (Gibco, Grand Island, NY). Female C3H/HeJ mice (Jackson Laboratory, Bar Harbor, ME), 4–6 weeks of age on arrival, were quarantined for at least 2 weeks and then inoculated s.c. with 5 × 10³ log phase tissue culture tumor cells, on the right flank. Randomly selected mice were tested and found to be free of adventitious murine viruses. All mice were housed 4–5 cage, in a temperature- and humidity-controlled facility with a 12-h light-dark cycle (lights on at 6:00 a.m. local time). Mice were provided standard mouse chow and water ad libitum. Studies were initiated 14 days after tumor inoculation when tumors were approximately 0.5 g. At this size, the tumors are well vascularized, do not exhibit central necrosis, and only rarely exhibit focal necrosis (19, 20). Treatments were routinely initiated between 7:00 a.m. and 9:00 a.m. local time.

Interleukin 1α and Chemotherapy Treatments. Recombinant human IL-1α was generously provided by Dr. Peter Lomedico (Hoffmann-La Roche, Nutley, NJ). The IL-1α used in these studies was highly purified (2.5 × 10³ D10 units/mg protein) and essentially free of endotoxin contamination (<0.125 EU/mg protein). The IL-1α was diluted in nonpyrogenic 0.9% NaCl containing 0.05% bovine serum albumin and administered in 0.2 ml, total volume, by i.p. injection. cis-Platinol (Bristol Laboratories, Syracuse, NY), indomethacin sodium trihydrate (Indocin; Merck and Co, West Point, PA), and dexamethasone (dexamethasone NaPO₄; ESI, Inc., Cherry Hills, NJ) were freshly prepared prior to use in sterile nonpyrogenic 0.9% NaCl and administered in 0.1–0.14 ml to mice by i.v. injection. In some experiments tumor perfusion was inhibited by applying a tourniquet (000 surgical silk) 1 h after cP treatment. Mice were anesthetized with Metapane (Pitman-Moore, Washington Crossing, NJ) prior to the application of the tourniquet, and it remained in place for up to 4 h (i.e., 5 h after cP treatment).

Clonogenic Tumor Cell Survival and Tumor Growth Inhibition. The in vitro cytotoxicity of cP with and without IL-1α was determined in mid-log phase monolayers of SCC VII tumor cells. Cells were washed once and exposed to drug in media without serum. At the end of the exposure period the monolayer was washed twice with media and then trypsinized. The cells were...
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washed twice more, counted, appropriately diluted, and plated out in complete medium at several cell densities. Plating efficiencies and surviving fractions were calculated from colony counts made at 7 days after plating (22). In some experiments tumor cells, treated with cP, were then held under hypoxic conditions before plating. Culture dishes were placed in an airtight chamber and subjected to 4 cycles of alternatively flushing with 95% N2 and 5% CO2 and evacuating by vacuum suction. The chambers were then maintained with 5% CO2 and 95% N2 for 4 h.

The effect of IL-1α and cP on the clonogenic tumor cellularity in RIF-1 and SCC VII solid tumors was determined by a modification (19-22) of the excision clonogenic cell survival assay described by Twentyman (27). Tumors were aseptically excised 24 h after IL-1α treatment, weighed, minced with scissors, and incubated with an enzyme cocktail (trypsin, type 3, 0.375 mg/ml; collagenase, type 2, 0.75 mg/ml; and DNAase, 0.1 mg/ml; all from Sigma Chemical Co., St. Louis, MO) in Hank's balanced salt solution, at room temperature, with constant agitation, for 45 min. In a typical experiment, tumors were resected, weighed, and bisected, and weighed tissue from 2 to 3 tumors was pooled prior to mincing. Similarly prepared suspensions from untreated control tumors were included in each experiment. The enzyme-dissociated cell suspension was filtered through sterile gauze and centrifuged. The cells were resuspended in fresh media containing 15% serum, washed twice, counted, diluted, and plated out, at several dilutions in 60-mm tissue culture plates. Control tumor cell yields were routinely 1-2 × 10^6 trypan blue-excluding cells/g tissue. The cultures were incubated for 7 days, at which time the colonies were counted and the number of clonogenic cells/g tissue was determined. Surviving fractions were taken as the ratio of clonogenic cells/g in treated and control tumors.

In tumor growth inhibition experiments, tumor diameters were determined at regular intervals after drug treatment by caliper measurements. Tumor volumes were estimated from:

\[ \frac{d_1 \times d_2 \times d_3}{2} \]

where \(d_1, d_2,\) and \(d_3\) are 3 right-angle diameters (22) and are expressed as a fraction of the tumor size at the time of first treatment. Tumor volumes were approximately 0.5 cm^3 at the beginning of treatment. Regrowth delay, estimated as the difference in time for control and treated tumors to reach 4 times pretreatment size, was expressed as a multiple of the calculated volume doubling time for regrowing tumors.

Statistical Analysis. Analysis of variance was used to determine if the observed treatment effects could be accounted for by chance alone. Where significant treatment effects were detected, the Newman-Keuls multiple range test was used to test the significance of differences between group means. A P value of 0.05 or less was considered adequate to reject the null hypothesis (28).

RESULTS

Clonogenic cell killing in RIF-1 tumors by combinations of IL-1α and cP was highly schedule (\(P < 0.001\)) and IL-1α dose (\(P < 0.001\)) dependent (Fig. 1A). Although treatment with IL-1α at 6 h after cP (6 mg/kg) resulted in more clonogenic cell kill than cP alone, a similar treatment at 8 h after cP produced only additive effects (Fig. 1A). When cP was administered after IL-1α clonogenic cell survival increased with time. When cP was given 2 h after IL-1α, a time when tumor perfusion is maximally suppressed (21), survival was similar to that for cP alone. Time course studies were not carried out with the other tumor models. When cP was given 1 h before IL-1α, the efficacy of this combination was highly IL-1α dose dependent (Fig. 1B). With both 4 or 6 mg/kg cP maximal effects were seen with approximately 10 μg/kg IL-1α. Dose-dependent decreases in clonogenic cell survival were also seen after IL-1α alone (Fig. 1B). Although several experiments with IL-1α at 25 μg/kg were conducted, the IL-1α dose response was not extensively studied in cP-treated SCC VII tumors.

The kinetics of clonogenic cell killing after cP with and without IL-1α is shown in Fig. 2. IL-1α (25 μg/kg) was administered 1 h after cP (6 or 8 mg/kg) treatment. Tumors were harvested, and clonogenic cell survival was determined at intervals up to 24 h after cP alone or after the cP plus IL-1α combination. Maximal clonogenic cell kill after cP alone was seen by 8 h after treatment, with some recovery.
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When IL-1α was given 1 h after cP, increased clonogenic cell kill was apparent within 2–3 h after the combination. Little or no recovery between 3 and 24 h after treatment was seen at either the 6 or 8 mg/kg cP dose levels. These data also provided an indication that the response to the combinations was cP dose dependent.

The effect of IL-1α (25 μg/kg) on the cP dose-dependent clonogenic cell kill in SCC VII, RIF-1, and RIF-R1cp tumors is shown in Fig. 3. Also shown is the effect of IL-1α (1000 units/ml for 4 h) on the cytotocicity of cP in RIF-1 cells in vitro (Fig. 3d). D₅₀ and 95% confidence limits were calculated (29, 30) and are shown in Table 1.

The median effect principle (29) was applied to test the hypothesis that cP and IL-1α (1 h after cP) produced a synergistic antitumor effect (Fig. 4). Data from Figs. 1 and 3 were used in the combination indices calculations as described previously (29). Additionally, data from SCC VII tumors treated with IL-1α (12.5 μg/kg) and cP (4 and 8 mg/kg) (not shown above) were also included in the analysis. Thus, mean responses with 15 and 7 combinations in RIF-1 and SC VII tumors, respectively, were used in the calculations. Lines were fitted to the data by linear (RIF-1) and exponential (SCC VII) regression analysis. Combination indices of less than 1 (synergy) were seen for both tumor models when the combination produced at least a 90% effect (i.e., 10% survival).

Although cP (6 mg/kg i.v.) produced significant RIF-1 tumor growth inhibition, IL-1α (25 μg/kg i.p.) had little effect (Fig. 5). The regrowth delay (7 days) after cP was approximately twice the volume doubling time of regrowing tumors. cP (6 mg/kg) and IL-1α (25 μg/kg 1 h after cP) produced a regrowth delay of approximately 7 volumetric doubling times (i.e., 22 days). These data are qualitatively consistent with the clonogenic cell survival data presented above and the conclusion that cP and IL-1 have synergistic antitumor activity. RIF-1 tumor growth inhibition produced by cP and IL-1α was also schedule dependent. When cP was given 4 h after IL-1α, tumor regrowth patterns were similar to those seen after cP alone.

Although IL-1α may stimulate endothelial cells and macrophages to produce prostaglandins, such responses may not be relevant for the synergistic antitumor activity of IL-1α and cP since indomethacin

<table>
<thead>
<tr>
<th>Treatments</th>
<th>SCC VII</th>
<th>RIF-1</th>
<th>RIF-R1cp</th>
</tr>
</thead>
<tbody>
<tr>
<td>cP</td>
<td>2.3 (0.2, 2.5)</td>
<td>2.00 (1.4, 2.7)</td>
<td>5.2 (4.0, 6.8)</td>
</tr>
<tr>
<td>IL-1α</td>
<td>0.018 (0.014, 0.022)</td>
<td>0.026 (0.018, 0.034)</td>
<td>ND</td>
</tr>
<tr>
<td>cP + IL-1α</td>
<td>0.81 (0.4, 1.3)</td>
<td>0.45 (0.32, 0.56)</td>
<td>1.4 (0.9, 1.9)</td>
</tr>
</tbody>
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a D₅₀ in mg/kg (95% confidence limits).
b Not done.
c IL-1α (10 μg/kg) administered 1 h after cP.
d Significantly different from cP alone.
Dexamethasone (10 mg/kg i.v.) was administered with cP (i.e., 60 min dexamethasone alone, indomethacin alone, and cP alone, respectively). Surviving fractions after cP, ligation, and reperfusion were reported within 2 h after i.p. administration of the cytokine perfusion, and reduced high-energy phosphate levels in RIF-1 tumors before IL-1α.

Qualitatively, indomethacin had no discernible effect on the acute effect on the clonogenic cell kill induced by the combination (Fig. 6). In other similarly treated mice the tourniquet was released and 2 h of "reperfusion" was permitted before the tumors were harvested for clonogenic cell survival assay. In controls (no cP pretreatment), 2 h of "reperfusion" had little effect on clonogenic cell survival in tumors ligated for 2 or 4 h. In cP-pretreated tumors (4 or 6 mg/kg), increased clonogenic cell kill was seen after "reperfusion."

**DISCUSSION**

Interleukin 1 can profoundly affect the pathophysiology of murine solid tumors. Vasodilation and intravascular congestion were seen within 1–2 h after IL-1α treatment, while microvascular injury and acute hemorrhagic necrosis are grossly evident 2–3 h later (19–21). Although IL-1α is known to stimulate macrophages to produce TNF (31) and the hemorrhagic response after IL-1 is macroscopically similar to that produced by TNF, host cell infiltration and fibrin clot deposits, characteristic of the TNF response (32), were not seen in our tumor models during the first 4–6 h after IL-1α treatment (20, 33). Furthermore, since anti-murine TNF monoclonal antibody did not inhibit IL-1α-induced hemorrhagic necrosis in RIF-1 tumors (34), it is likely that TNF is not a proximal mediator of IL-1α-induced antitumor responses. Microvascular responses resulted in decreases in tumor perfusion and reduced high-energy phosphate reserves within 1–2 h after IL-1α treatment. IL-1α-induced tumor-specific microvascular deposits, characteristic of the TNF response (32), were not seen in our tumor models during the first 4–6 h after IL-1α treatment (20, 33). Furthermore, since anti-murine TNF monoclonal antibody did not inhibit IL-1α-induced hemorrhagic necrosis in RIF-1 tumors (34), it is likely that TNF is not a proximal mediator of IL-1α-induced antitumor responses. Microvascular responses resulted in decreases in tumor perfusion and reduced high-energy phosphate reserves within 1–2 h after IL-1α treatment. IL-1α-induced tumor-specific microvascular
injury and hemorrhagic necrosis, seen in sarcomas (19–21), adenocarcinomas (21, 35) and squamous cell tumor (present study) models, can be inhibited by corticosteroids (33). The antitumor activity of mitomycin C and porfiromycin, two agents previously shown to be preferentially cytotoxic to murine hypoxic tumor cells, was markedly increased by IL-1α in a time- and dose-dependent fashion without an attendant increase in marrow toxicity (22, 23). In addition, the in vivo clonogenic cell kill by SR 4233, a potent hypoxic cell cytotoxin and radiosensitizer, was also markedly increased by a subsequent IL-1α treatment (36). These later findings together with the results from recently reported radiobiological studies (37) in RIF-1 and SCC VII tumors suggest that transient tumor hypoxia may not be unusual after IL-1α treatment.

Median effect analysis indicated that combinations of IL-1α and CP produced synergistic antitumor activity in RIF-1 and SCC VII tumors. Previous studies in SCC VII (24, 25) and colon 26 tumors (38) suggested that IL-1α and CP may produce more than additive tumor growth inhibitor effects, but since in much of the previous work (38) growth inhibition of highly immunogenic tumors was used as the therapeutic end point, immune responses might have masked IL-1α-induced increases in cellular chemosensitivity. Our findings of increased clonogenic cell kill by 2 h after the CP plus IL-1α combination would suggest that IL-1α-induced modification of cellular CP cytotoxicity is a likely explanation of CP plus IL-1α synergistic antitumor activity in our models. Our findings that the CP plus IL-1α combination produced a marked increase in clonogenic cell killing in CP-resistant RIF-R1cp tumors is also consistent with this hypothesis. Although the mechanism of CP resistance in this cell line is not fully defined, it is highly resistant to CdCl2 but not to H2O2. This pattern is consistent with the conclusion that increased metalloethionine levels are responsible for increased CP resistance in the RIF-R1cp cell line (39). Since overexpression of metalloethionine is a significant factor in clinical resistance to platinum-containing drugs (40, 41), IL-1α might be useful for increasing the efficacy of chemotherapy strategies for CP-resistant tumors.

Although IL-1α dose dependencies for combinations of IL-1α and mitomycin C and IL-1α and CP were similar in RIF-1 tumors, the schedule dependency for IL-1α and CP indicates that CP-treated tumor cells may exhibit a wider window of vulnerability to the in vitro effects of IL-1α than do cells in tumors pretreated with mitomycin C (22, 23) or SR4233 (36). Mitomycin C and SR 4233 schedule dependency is likely related to drug clearance rates and the kinetics of IL-1α-induced tumor hypoxia, since both agents are known to be activated more efficiently (42, 43) and to be more cytotoxic (42, 44) in hypoxic cells. Hypoxia-mediated increases in CP sensitivity are an unlikely explanation for the synergistic antitumor activity of CP plus IL-1α, since hypoxia has not been shown to increase CP sensitivity in vivo (26, 27).

Although IL-1 is known to stimulate phospholipase activity (45) and the synthesis of vasoactive and immunosuppressive eicosanoids by endothelial cells, fibroblasts, macrophages, and tumor cells (45–49), indomethacin had little or no effect on IL-1α-induced hemorrhagic necrosis or the synergistic antitumor activity of IL-1α and CP in SCC VII and RIF-1 tumors. These results are in contrast with those reported previously (50), where indomethacin increased the antitumor activity of IL-1 in some models. Such differences might be due to the difference in method of indomethacin administration or, since prostaglandins are immunosuppressive, the result of using immunogenic tumors. Products of the lipoxygenase pathways have been implicated in IL-1-induced hemodynamic toxicities (51, 52), but the possibility that this pathway may play a role in IL-1α-induced tumor microvascular injury and synergistic antitumor activity with CP remains to be confirmed.

Adrenal responses exert a negative feedback on IL-1-induced activities (33), and exogenous corticosteroids have been shown to inhibit IL-1α-induced hemorrhagic necrosis in solid tumors (31). In the present studies, dexamethasone not only inhibited the IL-1α-induced hemorrhagic necrosis but also inhibited CP plus IL-1α synergistic antitumor activity. Although both observations could be produced by a similar IL-1α-stimulated activity, it seems unlikely that the hemorrhagic response could play a seminal role in the synergistic activity of CP plus IL-1α, since hemorrhagic necrosis was not seen until after increased clonogenic cell kill was evident.

Ischemic hypoxia produced by physical occlusion of tumor vascular supply after CP treatment was not sufficient to increase CP clonogenic cell killing in vivo. These results not only support our in vitro data but also suggest that trapping of drug in the tumor after IL-1α treatment may also be an unlikely explanation for the synergistic antitumor activity of CP plus IL-1α. The increased clonogenic cell kill seen when sampling was delayed until after release of the clamp would be consistent with the hypothesis that metabolic responses subsequent to release of the clamp led to increased CP sensitivity. Oxidative injury after reperfusion of ischemic normal tissue has been well documented in liver (53), heart (54), and brain (55, 56). Although the kinetics of the tumor blood flow perturbations and the kinetics of clonogenic cell killing after CP plus IL-1α combinations would argue against a “reperfusion oxidant injury” as an explanation for the synergistic antitumor activity of CP plus IL-1α, it is well known that IL-1α can stimulate neutrophils, macrophages, and endothelial cells to produce superoxide, nitric oxide, and hydrogen peroxide (57–60). These oxidants can result in lipid peroxidation (55, 61), mitochondrial membrane depolarization and Ca2+ mobilization (62), phospholipase activation (45), poly-ADP ribose polymerase activation (63), reduced ATP synthesis (62), DNA base alterations (64), and DNA strand breaks in tumor cells (63–65). Prostaglandins can potentiate stimulated superoxide release (66), and TNF, known to be induced by IL-1 (31), can reduce the ability of tumor cells to accumulate sublethal radiation damage (67). Catalase partially inhibited this latter activity, suggesting that oxidant DNA injury may play an important role in TNF radiosensitization in vitro. TNF is thought not to play a role in the initiation of IL-1α-induced hemorrhagic necrosis (34), but its role in the antitumor activity produced by CP and IL-1α is not known. CP has also been shown to stimulate macrophages to produce TNF and IL-1 (68), and several chemotherapy agents, including CP, were synergistic with TNF in vitro (69, 70).

Although much is known about the metabolic effects of superoxides and peroxides in cells, the effect of these oxidants on CP cytotoxicity in vivo or in vitro has not been well studied. Combinations of CP and SR4233, a bioreductively activated superoxide generator (43) in hypoxic cells (71), produced more than additive cytotoxicity in hypoxic tumor cells in vivo (72). Since oxidant stress can reduce mitochondrial membrane potential (62), Krebs cycle enzyme activities (73), and ATP synthesis (62, 63), it is conceivable that the disruption of an energy-dependent repair process provides an explanation for the antitumor activity of CP and IL-1α. Mitochondrial injury (74) and inhibition of glycolysis (75) after CP was previously shown to increase CP cytotoxicity in some systems. Since we showed that IL-1α treatment can also lead to prompt depletion of high-energy phosphate reserves of tumors (19, 20) in vivo, it is conceivable that the schedule-dependent synergistic antitumor activity of CP and IL-1α could have a similar mechanism.

It is well known that IL-1 can result in the stimulation of antioxidant pathways in many normal tissues (76–78). Such effects may
result from oxidative stress (76) but, up to 72 h they may be required for expression (76, 79, 80). The activation of antioxidant pathways after IL-1α-induced oxidative stress might provide an explanation for the protective effects of IL-1 against oxidative injury in some systems (76). IL-1 can stimulate metallothionein synthesis in some (e.g., liver, bone marrow, thymus) but not in all tissues (78, 81–83). These cysteine-rich proteins are associated with cP resistance (40, 41), but they may also exhibit antioxidant properties (84, 85). Little is known about the stimulation of metallothioneins and other antioxidants by IL-1α in solid tumors. In vitro, IL-1α increased metallothionein gene expression in human liver tumor cells and HL-60 cells, but only after a 12–24-h lag (86). Although IL-1α-induced chemosensitization was essentially complete by 6 h after IL-1α in our models, IL-1α or corticosteroid stimulation of antioxidant pathways might transiently increase cP resistance and reduce the efficacy of a subsequent treatment. High metallothionein levels are not likely to be a barrier to IL-1-mediated cP chemosensitization, since IL-1 and cP exhibited more than additive clonogenic cell kill in tumors produced with CdCl2-resistant Rif-IR1γp cells. Additional studies are needed to address these and other scheduling questions.

In addition to the pathophysiological effects of IL-1 in solid tumors, this cytokine may offer another potential clinical advantage, since it cP chemosensitization, since IL-1α or corticosteroid stimulation of antioxidant pathways might transiently increase cP resistance and reduce the efficacy of a subsequent treatment. High metallothionein levels are not likely to be a barrier to IL-1-mediated cP chemosensitization, since IL-1 and cP exhibited more than additive clonogenic cell kill in tumors produced with CdCl2-resistant Rif-IR1γp cells. Additional studies are needed to address these and other scheduling questions.

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