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In Vivo Chemosensitization by Misonidazole in Sensitive and Resistant Tumor Lines[1]

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ABSTRACT

In an attempt to evaluate whether the radiation sensitizer misonidazole (MISO) could enhance the responsiveness of chemoresistant tumors, MISO was combined with 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) and/or 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) for the treatment of BALB/c × DBA/2 F_1 (hereafter called $CD2F_1$) and C3H/HeJ mice bearing nitrosourea-resistant L1210/BCNU or KHT/CCR tumors, respectively. To determine whether comparable degrees of enhancement could be achieved in sensitive and resistant tumor lines, the magnitude of chemosensitization produced by treating the resistant tumors with the MISO-nitrosourea combinations was compared to the chemopotentiation produced in similarly treated nitrosourea-sensitive tumor lines from which the resistant lines had been derived. As evidenced by increased cure probabilities, the addition of MISO [5.0 mmol/kg (1.0 mg/g)] significantly potentiated the response of the parental nitrosourea-sensitive L1210/0 tumor to a 20-mg/kg dose of CCNU. When combined with doses of CCNU lower than 20 mg/kg or with BCNU, MISO failed to significantly modify the response of the L1210/0 tumor. Significant chemosensitization also was evident when 2.5- and 1.25-mmol/kg doses of MISO were used in combination with CCNU at 20 mg/kg. The effectiveness of BCNU and CCNU against the nitrosourea-resistant L1210/BCNU tumor was not significantly improved by MISO (5.0 mmol/kg), even when the sensitizer was combined with doses of nitrosoureas approaching 10% lethal dose (60 days) concentrations. In contrast, the effectiveness of CCNU against the parental KHT and resistant KHT/CCR tumors, assessed using a tumor regrowth assay, was equally enhanced by simultaneous MISO treatment. Therefore, one cannot safely predict the extent of enhancement which might result from the addition of MISO to a chemotherapeutic regimen based solely on the responsiveness of the tumor to the chemotherapy drug(s) alone.

INTRODUCTION

The response of several experimental tumor models to conventional chemotherapeutic agents has been augmented by combination treatment with certain nitroimidazole radiosensitizers, most notably MISO[3] (for review, see Refs. 4 and 14). In many *in vivo* model systems, the enhancement of antitumor effectiveness has exceeded the concomitant increase in normal tissue toxicity associated with such combinations. The potential of implementing this combination therapy for the treatment of human cancers is currently being assessed in clinical trials. These clinical trials will evaluate the efficacy of nitroimidazole chemosensitization against tumors which, as a result of histological type or clinical stage, are considered minimally responsive to conventional therapies.

To date, there is a paucity of chemosensitization data comparing the responsiveness of sensitive and resistant animal tumors. However, it has been suggested that chemoresistant tumors might well be refractory to enhancement by MISO (2). It is therefore important to address experimentally whether comparable degrees of chemosensitization can be achieved in resistant tumors. Consequently, in the present series of experiments, we have evaluated and compared the effectiveness of combinations of nitrosourea chemotherapeutic agents and MISO on sensitive and resistant sublines of 2 different murine tumor models.

MATERIALS AND METHODS

Drug Preparation

BCNU and CCNU, obtained from Dr. Robert Engle (Drug Research and Development Branch, National Cancer Institute), were initially dissolved in absolute ethanol. Immediately before injection, BCNU was diluted to its final concentrations with a 0.9% NaCl solution, while the CCNU ethanol stock was diluted 10-fold in a 0.3% solution of hydroxypropyl cellulose in 0.9% NaCl. MISO, received from Dr. Ven Narayanan (Drug Synthesis and Chemistry Branch, National Cancer Institute), was dissolved in 0.9% NaCl solution at a concentration of 20 mg/ml. All injections were i.p., and all drug combinations were given simultaneously.

Tumor Models and Response

L1210 Leukemia. The parental L1210/0 and the nitrosourea-resistant L1210/BCNU (9) cell lines were kindly provided by Dr. G. P. Wheeler of the Southern Research Institute, Birmingham, Ala. Male BALB/c × DBA/2 F_1 (hereafter called $CD2F_1$) mice, 6 to 8 weeks of age, were given i.p. injections with 10^5 L1210/0 or L1210/BCNU tumor cells harvested from the peritoneal cavities of donor mice on the seventh day postimplantation. Forty-eight hr after implantation, the animals were randomly assigned to experimental or control groups and treated. Animals treated with nitrosourea alone also received an i.p. injection of 0.9% NaCl solution equivalent in volume to that administered to animals treated with MISO. The animals then were observed daily for deaths. Median survival time was determined to the nearest 0.5 day. Animals which were alive 60 days after tumor implantation were considered cured.

KHT Sarcoma. This tumor, which originally arose spontaneously (3), was transplanted into the left hind limb of female C3H/HeJ mice by injecting 2 × 10^5 cells i.m. Single-cell suspensions for the tumor cell transfer procedure were prepared as described previously (18). After 7 days, when the tumors had grown to a weight of 0.2 to 0.3 g, the animals were allocated randomly into groups and treated or kept as controls as

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[3] The abbreviations used are: MISO, misonidazole; BCNU, 1,3-bis(2-chloroethyl)-1-nitrosourea; CCNU, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea.

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required. The response of the tumors to the chemotherapy administered either alone or in combination with the sensitizer was assessed using a tumor regrowth assay (15, 17). After treatment, each tumor was measured daily by passing the tumor-bearing leg through a plastic rod with increasing diameter holes. The smallest hole the tumor-bearing leg would pass through was recorded. This size measurement was converted to a tumor weight using a calibration curve obtained by excising and weighing the tumors from tumor-bearing legs of various sizes as has been described previously (15, 17). The time for each tumor to grow to 4 times the starting weight was recorded, and the median time for the tumors of each group of mice to reach this endpoint was calculated. Confidence intervals about the median were determined using nonparametric statistics (8).

RESULTS

L1210 Leukemia. The median day of death of untreated control animals was not significantly different for animals grafted i.p. with 10^5 cells from the parental L1210/0 or the resistant L1210/BCNU subline as reported previously (10). (Table 1; Chart 1). As shown in Chart 1, animal mortality was not significantly altered following treatment 2 days after tumor implantation with doses of MISO up to 1.0 mg/g (5.0 mmol/kg). Although treatment with BCNU on Day 2 increased the life span of recipients bearing L1210/0 or L1210/BCNU in a dose-dependent fashion (Table 1), the antitumor effectiveness of BCNU was significantly greater against the sensitive L1210/0 line (12). For example, whereas 29% of mice bearing the L1210/0 tumor were cured following treatment with a single 20-mg/kg dose of BCNU on Day 2, cures were never produced in L1210/BCNU-bearing animals even at doses of BCNU as high as 40 mg/kg. The antitumor efficacy of BCNU against the L1210/0 and the L1210/BCNU subline was not significantly improved by the addition of MISO to the treatment protocol.

In addition to demonstrating marked resistance to the cytotoxic effects of BCNU, L1210/BCNU tumor cells exhibit cross-resistance to other nitrosoureas, including CCNU (11). Since the magnitude of MISO enhancement has been shown to be greater for CCNU than BCNU (6), the responses of the 2 L1210 tumor lines to CCNU alone and in combination with MISO were determined and compared to those obtained in the BCNU-MISO experiments. As with BCNU, increasing doses of CCNU produced progressive improvements in the cure probability and the median life span for animals bearing either tumor subline. Comparable with the BCNU results, cures were only realized in the L1210/0 groups, even though doses approaching the lethal dose to 10% of the mice in 60 days were administered to the L1210/BCNU animals (Table 2). As with BCNU, MISO did not significantly enhance the response of the L1210/BCNU tumor at any dose of CCNU, up to approximately the lethal dose to 10% of the mice in 60 days. The effectiveness of low doses of CCNU against the L1210/0 tumor was likewise not enhanced by combination with MISO. However, relative to treatment with a 20-mg/kg dose of CCNU alone, a significantly improved cure probability (91 *versus* 25%) was produced in L1210/0 animals treated with CCNU (20 mg/kg) and MISO (1.0 mg/g) (Table 2; Chart 2*a*). Furthermore, when combined with CCNU (20 mg/kg), reduced MISO doses of 0.5 and 0.25 mg/g also produced enhanced cure rates. In spite of the favorable responses produced in the sensitive parental L1210/0 line, MISO failed to modify the response

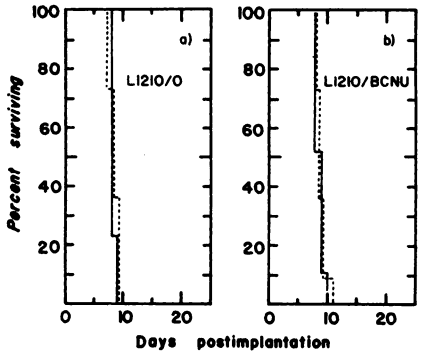

Chart 1. Cumulative mortality plots for CD2F$_1$ mice given i.p. injections with 10^5 L1210/0 or L1210/BCNU cells. Mortality of untreated controls (——) and animals treated with a single 1.0-mg/g dose of MISO (- - - -) 2 days after inoculation with L1210/0 (*a*) or L1210/BCNU (*b*) cells.

Table 1

Comparative response of L1210/0 and L1210/BCNU cells to treatment on Day 2 with BCNU alone or combined with MISO

Cell line	No. of Experiments	Dose BCNU (mg/kg)	MISO (0.5 mg/g)	Toxicity[a]	% of ILS[b]	Cures (60-day survivors/ total)
L1210/0	6	0	–			0/43
	5	0	+	0/7	0	0/38
	2	20	–		81	4/14
	2	20	+		100	5/14
	3	30	–		88	7/19
	2	30	+		100	7/14
	2	40	–	0/7	100	7/14
	2	40	+	1/14	138	8/14
L1210/BCNU	6	0	–			0/43
	3	0	+	0/7	0	0/21
	2	20	–		29	0/14
	2	20	+		29	0/14
	3	30	–		41	0/19
	2	30	+		41	0/14
	2	40	–	0/7	41	0/14
	2	40	+	1/14	65	0/14

[a] Number of non-tumor-bearing animals dying within 60 days of treatment per total number treated.
[b] Percentage of increase in life span (dying animals only) calculated as

$$\frac{\text{MST (treated)} - \text{MST (control)}}{\text{MST (control)}} \times 100$$

where MST is median survival time.

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Table 2

Comparative response of L1210/0 and L1210/BCNU cells to treatment on Day 2 with CCNU alone or combined with MISO

Cell line	No. of Experiments	Dose CCNU (mg/kg)	MISO (mg/g)	Toxicity[a]	% of ILS[b]	Cures (60-day survivors/total)
L1210/0	1	10	0		63	0/7
	1	10	0.5		75	0/7
	2	15	0		113	3/16
	2	15	0.5		113	5/17
	4	20	0		113	9/36
	2	20	0.25		125	11/17
	4	20	0.5		113	22/35
	1	20	1.0	0/9		10/11
L1210/BCNU	1	10	0		0	0/7
	1	10	0.5		0	0/7
	1	20	0		38	0/7
	1	20	0.5		50	0/7
	2	30	0		65	0/17
	2	30	0.5		65	0/17
	3	40	0	0/7	65	0/28
	3	40	0.5	0/7	65	0/28
	1	40	1.0	4/9	65	0/11

[a] Number of non-tumor-bearing animals dying within 60 days of treatment per total number treated.
[b] Percentage of increase in life span (dying animals only) calculated as

$$\frac{\text{MST (treated)} - \text{MST (control)}}{\text{MST (control)}} \times 100$$

where MST is median survival time.

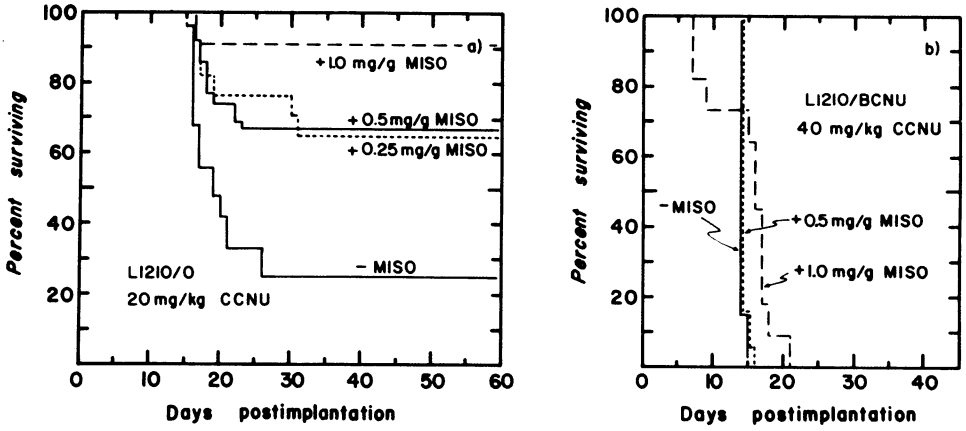

Chart 2. *a*, mortality plots for L1210/0-bearing mice treated with a 20-mg/kg dose of CCNU alone or combined with MISO (1.0, 0.5, or 0.25 mg/g); *b*, response of L1210/BCNU-bearing mice to treatment with a 40-mg/kg dose of CCNU or with a 40-mg/kg dose of CCNU and a 1.0- or 0.5-mg/g dose of MISO.

of L1210/BCNU cells to CCNU, even at maximally tolerated doses (Chart 2*b*).

KHT Sarcoma. A CCNU-resistant subline of the KHT sarcoma (KHT/CCR) was induced by treating tumor-bearing animals with a 20-mg/kg dose of CCNU, transplanting the tumors following regrowth, and then retreating with CCNU once solid tumors had been reestablished. This procedure was repeated at each passage, and Chart 3 shows the effectiveness of a 20-mg/kg dose of CCNU as a function of tumor passage number. The data show that the time to grow to 4 times the starting size decreased with passage number such that by 6 passages no difference in response between untreated tumors and those exposed to CCNU (20 mg/kg) could be detected. CCNU pretreatment was discontinued at passage 8 and, as can be seen in Chart 3, resistance to CCNU has remained stable for at least 15 subsequent passages.

Over a range of CCNU doses, this KHT subline was considerably more resistant than the parental line to CCNU treatment (Chart 4). For example, compared to untreated control tumors, a 30-mg/kg dose of CCNU led to no growth delay in the resistant cell line and a 13-day delay in the parental line. However, unlike

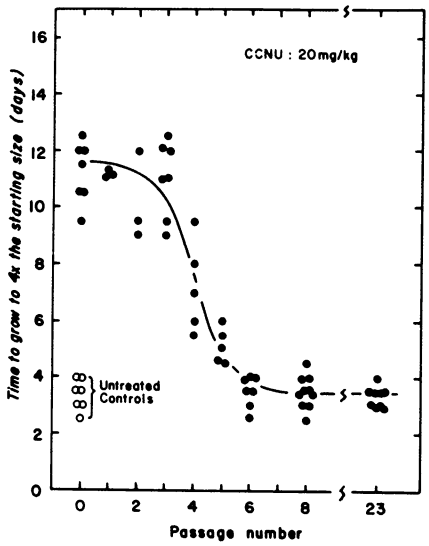

Chart 3. Induction of CCNU resistance in the KHT sarcoma by repeated sequential treatments with a 20-mg/kg dose of CCNU as described in text. CCNU exposures were stopped at passage 8. *Points*, single animals.

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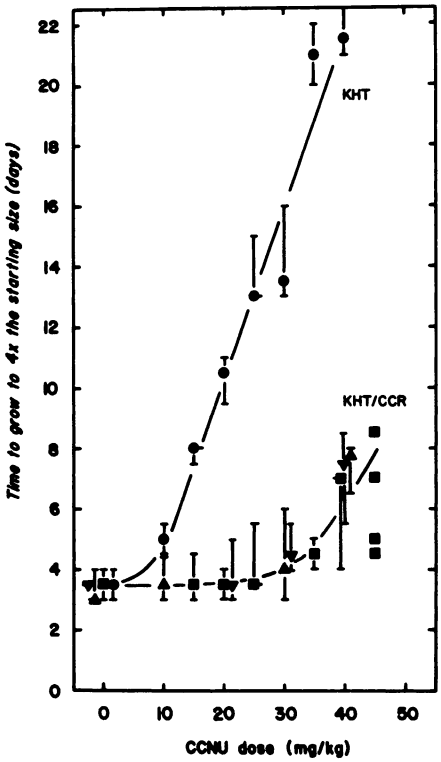

Chart 4. Relative response of KHT or KHT/CCR sarcoma-bearing C3H mice to a range of CCNU doses. The data shown are the median tumor responses of 7 to 10 mice with 98% confidence limits calculated using nonparametric statistics (8). *Points* shown for CCNU doses of 45 mg/kg represent individual tumors. This treatment resulted in 50% toxicity in the animals. ●, ▲, ■, ▼, separate determinations.

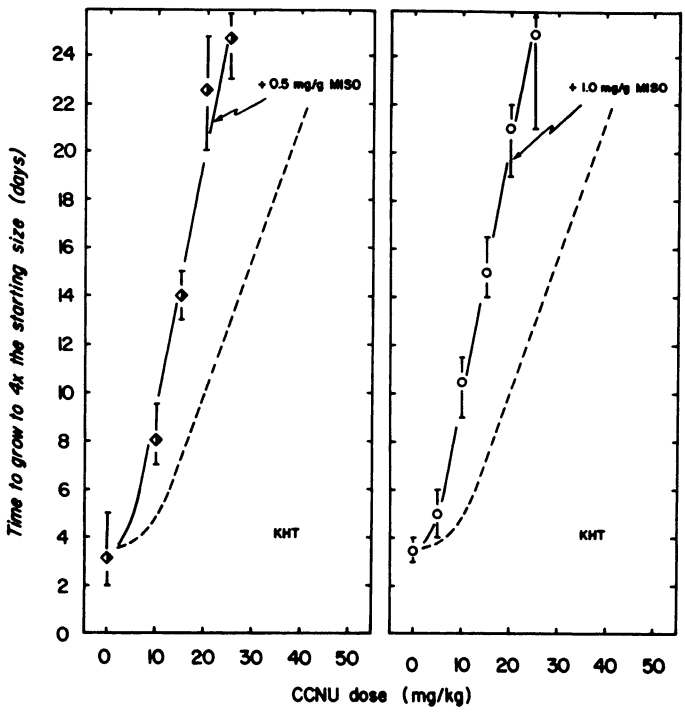

Chart 5. Response of the parental KHT sarcoma line to simultaneous combinations of CCNU and a 0.5- or 1.0-mg/g dose of MISO. Data shown are as described in Chart 4. ----, response of KHT sarcomas to CCNU alone, redrawn from Chart 4 for comparison.

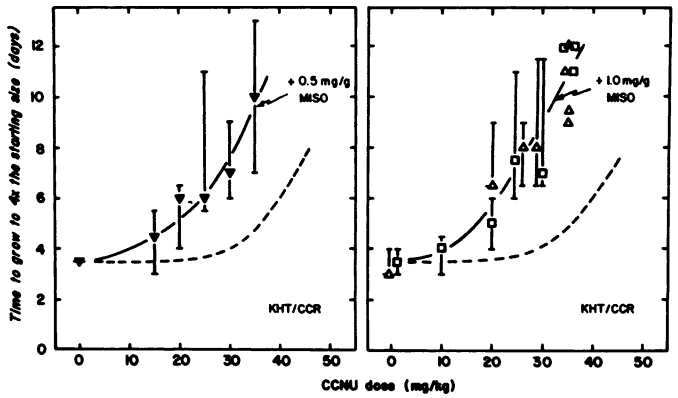

Chart 6. Efficacy of the combination of CCNU and MISO in the CCNU resistant subline KHT/CCR. The responses to CCNU plus a 0.5- or 1.0-mg/g dose of MISO are illustrated. *Points* are as described in Chart 4. ----, response of the KHT/CCR tumor to CCNU alone (redrawn from Chart 4).

the results observed in the L1210 studies, the addition of MISO at doses of 0.5 or 1.0 mg/g enhanced the response to CCNU in both the parental tumor line (Chart 5) and the CCNU resistant line (Chart 6). In fact the enhancement ratio (the dose of CCNU divided by the dose of CCNU plus MISO to yield the same tumor effect) was found to be 1.9, in both the KHT and KHT/CCR tumor lines following combination treatment with 0.5- and 1.0-mg/g doses of MISO, respectively.

DISCUSSION

The current investigations were designed to determine whether the chemotherapeutic response of chemoresistant tumors could be augmented by combination treatment with MISO. This question was evaluated by using 2 tumor model systems for which sublines resistant to BCNU and/or CCNU were available. In the L1210 murine leukemia system, the addition of MISO (1.0, 0.5, and 0.25 mg/g) significantly enhanced the response of the nitrosourea-sensitive parental line L1210/0 to a 20-mg/kg dose CCNU as indicated by improved cure rates but failed to significantly modify the response to lower doses of CCNU or BCNU. This differential enhancement of CCNU activity relative to BCNU substantiates earlier observations in several other tumor model systems, indicating that the enhancement by MISO is greater in animals treated with CCNU than in those treated with BCNU (5–7, 14, 16). This is clearly demonstrated by comparing the response of the L1210/0 cells treated with MISO (0.5 mg/g) combined with approximate isoeffect doses of BCNU and CCNU (Charts 1*c* and 2*a*). The addition of MISO improved the CCNU cure rate by a factor of 2.5 (25 to 63%) whereas BCNU cure efficiency was only increased 1.3-fold (38 to 52%). The response of the resistant L1210/BCNU line to BCNU and CCNU was not modified by the addition of MISO at any concentration. In marked contrast to the observations made with the L1210 model, in the KHT sarcoma model an enhancement equivalent to that seen for the parental line (Chart 5) also was produced in CCNU-resistant tumors (Chart 6). In fact, enhancements of 1.9 resulted when CCNU was combined with a 0.5 or 1.0 mg/g dose of MISO for the treatment of either KHT tumor. The magnitude of enhancement achieved in these studies is consistent with previous reports of CCNU sensitization by MISO (4, 13, 14, 20).

The L1210/0 data indicate that chemosensitization is ex-

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pressed only when MISO is added to doses of nitrosoureas which alone reduce the viable tumor cell burden to extremely low levels (an average of ~2 tumor stem cells per animal). It is therefore possible that the responses of the sensitive and resistant ascites cells to CCNU are equally potentiated by MISO, but that the inability to reduce the L1210/BCNU tumor burden to near curative levels precluded the detection of chemosensitization in the resistant subline. To further evaluate whether comparable degrees of enhancement could be achieved in the sensitive and resistant L1210 leukemias, *in vitro* adapted cell lines were derived from the two *in vivo* tumors and were treated in suspension culture with CCNU alone or combined with MISO under aerobic and hypoxic conditions. Cell survival was subsequently determined using a soft agar cloning assay. The effectiveness of CCNU against L1210/0 cells was significantly enhanced by the addition of MISO (1.0 mg/g) under hypoxic conditions, while its efficacy against hypoxic L1210/BCNU cells was not modified by MISO.[4] These results indicate that the lack of chemosensitization in mice bearing the L1210/BCNU leukemia is due to inherent properties of the tumor cells and not to an inability to detect enhancement following MISO-CCNU treatment *in vivo*. This property is obviously not shared by the parental L1210/0 cells, which can be effectively sensitized by MISO *in vivo* and *in vitro*.

Likewise, this resistant property is not shared by KHT/CCR tumor cells which, like the sensitive KHT and L1210/0 tumors, can be potentiated by adding MISO to nitrosourea treatment. The differential effect of MISO in the 2 resistant tumor models most likely reflects differences in the basic underlying mechanism(s) of chemoresistance operative in the 2 cell lines. Since many resistance mechanisms have been identified (1) and since additional mechanisms frequently emerge from different induction protocols or continued tumor passage (19), it is likely that KHT/CCR and L1210/BCNU cells express different escape mechanisms. Consequently, MISO could preferentially sensitize one of the tumors to the nitrosoureas without influencing the response of the other.

In light of these considerations, it seems likely that examination of chemosensitization in resistant tumors or sublines will yield only a spectrum of response enhancements comparable to those already available from studies with more responsive tumor models. However, the use of tumor sublines in which differential chemosensitization by MISO has been established might prove to be an effective approach to investigate the mechanism(s) of chemosensitization.

In conclusion, one cannot safely predict the extent of enhancement which might result from the addition of MISO to a chemotherapeutic regimen based solely on the responsiveness of the tumor to the chemotherapy drug(s) alone. The mechanism of drug resistance operative in a cell line will certainly be an important variable influencing the magnitude of chemopotentiation by MISO.

[4] R. T. Mulcahy, N. L. Dembs, and G. A. Ublacker. Enhancement of nitrosourea cytotoxicity by misonidazole *in vitro*: correlation with carbamoylating potential, submitted for publication.

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