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Modulation of mitomycin C-induced multidrug resistance in vitro*

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Summary. A series of in vitro cytotoxicity studies were performed to achieve pharmacologic reversal of resistance to the alkylating agent mitomycin (MMC) in L-1210 leukemia cells. A multidrug-resistant (MDR), P-glycoprotein-positive cell line, RL-1210/.1 [11], was exposed to potential MDR modulators in the absence or presence of MMC. The following compounds did not reverse MMC-induced MDR: quinine, quinidine, lidocaine, procaine, dimethylsulfoxide (DMSO), dexamethasone, hydrocortisone, prednisolone, estradiol, and testosterone. Three agents were capable of reversing MMC resistance: progesterone, cyclosporin A, and verapamil. The R- and S-isomers of verapamil were equipotent, although they showed a 10-fold difference in cardiovascular potency (S >R). Some agents produced cytotoxic effects in MDR cells in the absence of MMC, including progesterone, quinine, and quinidine. The results suggest that R-verapamil and progesterone may have clinical utility in reversing MMC resistance in human tumors. Progesterone may be uniquely efficacious due to (a) its low toxicity in normal cells, (b) its selective cytotoxicity in MDR cells (in the absence of MMC), and (c) its ability to reverse MMC resistance in vitro. The findings also suggest that the P-glycoprotein induced by MMC differs from that induced by doxorubicin, which is highly sensitive to modulation by lysosomotropic amines such as quinine and quinidine.

Introduction

Mitomycin C (MMC) is a bifunctional alkylating agent that shows antitumor activity in a variety of adenocarcinomas [18]. Clinical resistance to MMC-containing drug regimens is typically encountered after the administration of 3–4 courses of combination chemotherapy in patients with gastric cancer [17], breast cancer [17], and colon cancer [21]. In vitro studies of MMC resistance have demonstrated the presence of unique cytosolic proteins, perhaps involving glutathione S-transferase enzymes [26]. In addition, resistant colon cancer cells express a cell-surface protein (relative mol. wt. 148,000 Da) and show reduced MMC-DNA cross-link formation [29]. Furthermore, cross-resistance to doxorubicin and numerous MMC-prodrugs has also been described in L-1210 leukemia cells selected for MMC resistance [18, 19]. Other studies have shown that enhanced enzymatic detoxification of MMC-induced free radicals in resistant cells involved glutathione peroxidase and S-transferase activities [12].

Our prior studies have shown that in a murine L-1210 leukemia cell line, MMC resistance was found to be associated with a classic multidrug resistance (MDR) phenotype involving the expression of (a) the membrane P-glycoprotein (relative mol. wt., 180,000 Da 15); (b) reduced drug accumulation; and (c) simultaneous cross-resistance to other natural-product chemotherapeutic drugs, including anthracyclines such as doxorubicin and the vinca alkaloids vincristine and vinblastine [11]. Sensitivity to MMC in the resistant cell line was partially restored by the calcium-channel antagonist verapamil.

In the current report, this MMC-resistant cell line, RL-1210/.1, was tested for sensitivity to a diverse group of potential modulators of MMC cytotoxicity. The results show that RL-1210/.1 cells are intrinsically more sensitive to growth-inhibitory effects produced by some potential modulators used in the absence of MMC. In addition, some modulators were shown to reverse resistance to other natural products but not to MMC. These results suggest several pharmacologic strategies for modulating MMC resistance due to the MDR phenomenon in vivo.

Materials and methods

Cell lines. Two L-1210 cell lines were maintained in suspension culture in 75-cm^2 plastic flasks. The culture medium RPMI-1640 was supple-

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Table 1. Growth-inhibitory effect of different drugs on mitomycin C-sensitive and -resistant L-1210 leukemia cells

Pharmacologic class (agents)	Concentration (μ*M*) reducing viable cells to 50% of control values[a]		Relative sensitivity
	L-1210	RL-1210/.1	
Corticosteroids:			
Dexamethasone	33	250	0.13
Estradiol	11	13	0.86
Hydrocortisone	50	62	0.81
Progesterone	230	10	23
Prednisolone	0.1	0.8	0.13
Testosterone	320	600	0.53
Membrane-active agents:			
Triton X-100 detergent	1.6×10^{-3}[b]	6×10^{-4}[b]	2.67
Lidocaine	250	310	0.81
Procaine	300	350	0.86
Polysorb (Tween)-80	0.008[c]	0.01[c]	0.80
Dimethylsulfoxide	0.1[c]	10.5[c]	<0.01
Antiarrhythmic agents:			
Verapamil (racemic)	30	25	1.2
Quinidine SO_4 (D-isomer)	45.5	6.7	6.8
Quinine HCl (L-isomer)	94.2	23.5	4.0
Miscellaneous agents:			
Cyclosporin A	62	62	1

[a] Continuous exposure to modulating drug (no mitomycin C used)
[b] Ratio of IC_{50} for L-1210 cells ÷ IC_{50} for L-1210/.1 cells
[c] Concentrations expressed as percentage (vol/vol) of final plating medium

mented with 1% glutamine and 10% heat-inactivated fetal bovine serum (Grand Islands Biologicals, N.Y.); 1% (vol/vol) penicillin (100 IU/ml) and streptomycin (100 μg/ml) were also added to yield a complete culture medium. In RL-1210/.1 cells, the culture medium was supplemented with MMC at a concentration of 0.1 μg/ml or 0.28 μM. The biologic characteristics of this P-glycoprotein-positive, MDR cell line have been described elsewhere [11].

Drugs and chemicals. Mitomycin C lyophilized powder (Mutamycin) was obtained from Bristol Laboratories (Evansville, Ind.) and doxorubicin lyophilized powder (Adriamycin) was obtained from Adria Laboratories (Columbus, Ohio). Cyclosporine A (SandImmune) was obtained as a 50-mg/ml commercial solution that also contained 650 mg/ml polyethoxylated castor oil (Cremophor) and 32.9% (vol/vol) alcohol. Hydrocortisone sodium phosphate (50 mg/ml, Hydrocortone) and prednisolone sodium phosphate (Hydeltrasol), 20 mg/ml) were obtained as sterile solutions from Merck, Sharpe and Dohme (West Point, Pa.). Progesterone sterile injection (50 mg/ml in sesame oil) was obtained from Goldline Laboratories (Ft. Lauderdale, Fla.) Dexamethasone Sodium Phosphate Injection (U.S.P.) was obtained as a sterile 4 mg/ml solution from Lyphomed, Inc. (Melrose Park, Ill.). Testosterone cypionate (Depo-Testosterone) was obtained as a sterile 100 mg/ml solution from the Upjohn Company (Kalamazoo, Mich.). Estradiol was obtained from Sigma Chemical Company (St. Louis, Mo.). Lidocaine HCl (1% sterile solution) was obtained from Astra Pharmaceutical Products (Westborough, Mass.), and procaine HCl (2% injection, Novacaine) was obtained from Winthrop-Breon Division of Sterling Drug (New York, N.Y.).

The pharmaceutical emulsifier Tween-80 (polyoxyethylene sorbitan monooleate) and the nonionic detergent Triton X-100 were obtained in liquid form from Sigma Chemical Company (St. Louis, Mo.) Quinine hydrochloride, quinidine sulfate, and chloroquine diphosphate were also obtained as powders from Sigma Chemical Company. Dimethyl sulfoxide (DMSO 99%, vol/vol) was obtained as the reagent-grade solution from J. T. Baker, Inc. (Phillipsburg, N.J.). Verapamil powder (racemic mixture) in a 2-ml glass ampule and the pure R- and S-isomers as powders were generously donated by Dr. Lee Nadler, Knoll Pharmaceuticals (Division of BASF Corporation, Whippany, N.Y.).

Growth-inhibition assays. Logarithmically growing cells were plated into 96-well plastic dishes (Falcon Plastics) at a density of 2,000/ml in 180 μl complete culture medium. Drugs were added at 10 X concentration (20 μl) and the cells were incubated for 6 days. Survival was assessed by the measurement of tetrazolium dye reduction to a colored formazan product [6]. In viable cells, the tetrazolium dye, 3-(4,5-dimethylthiazol-2-yl)-2,5-dipheryltetrazolium bromide (MTT) is reduced by mitochondrial reductases to yield a colored formazan that is solubilized in DMSO. The formazan product is quantitated spectrophotometrically by measuring absorbance at 540 nm in an automated, robotic photometer (BioMek, Beckman Instruments, Palo Alto, Calif.).

All drug exposures involved 3–6 determinations per experiment, and each experiment was repeated 1–2 times (6–12 determinations for each drug concentration tested). Unless otherwise indicated, all drugs were diluted in sterile 0.9% sodium chloride immediately prior to their addition to cells suspended in complete culture medium.

Relative resistance or sensitivity for modulating agents was defined as a ratio of the molar 50% inhibitory concentration (IC_{50}) in resistant cells divided by that in sensitive cells. Some experiments involved concurrent exposure to MMC and the modulating drug, using concentrations of the latter that did not generally induce growth inhibition of >50% in the absence of MMC. In each case, the percentage of growth inhibition for the combination was calculated by based on an arbitrar definition of 100% growth inhibition for the combination as being that level produced by a modulator used alone at a given concentration.

Results

Cytotoxicity of modulators used alone

RL-1210/.1 cells were selectively sensitive to a some agents that have previously demonstrated reversal of the MDR phenomenon in other resistant cell lines. The results (Table 1) show that progesterone, quinine, quinidine, and verapamil were significantly more cytotoxic to RL-1210/.1 cells than to parental cells. In resistant cells, progesterone produced cytotoxic effects at an IC_{50} 23 times lower than that required to induce toxic effects in sensitive cells. This contrasts with the resistance of RL-1210/.1 cells to all of the other corticosteroids tested, including dexamethasone, hydrocortisone, prednisolone, estradiol, and testosterone.

Triton X-100 was the only membrane-active agent that produced greater cytotoxic effects in resistant cells. With the other membrane-active agents, RL-1210/.1 cells displayed some degree of cross-resistance, for example, those cells showed 100-fold resistance to the dipolar solvent DMSO. Neither of the local anesthetics tested nor cyclosporin A showed any selective cytotoxicity toward resistant cells (Table 1).

In contrast, each of the antiarrhythmic agents tested was selectively cytotoxic to MMC-resistant cells. Relative sensitivity ratios ranged from 4 to 6.8 for the L- and D-isomers of quinine, respectively. Interestingly, both optical isomers of the calcium-channel antagonist verapamil were also roughly equipotent in terms of cytotoxicity to resistant cells results not shown.

Table 2. Modulation of mitomycin C resistance in L-1210 cells in vitro[a]

Agent (concentration)	Mitomycin C IC_{50}[b]		Relative resistance[c]
	L-1210	RL-1210/.1	
Mitomycin C	0.08	0.83	10.4
Corticosteroids:			
Hydrocortisone (10 μM)	0.07	0.63	9
Progesterone (10 μM)	0.07	0.18	2.6
Membrane-active agents:			
Lidocaine (100 μM)	0.08	0.56	7
Polysorb (Tween)-80 (.01%, vol/vol)	0.08	0.017	0.2
Antiarrhythmic agents:			
Verapamil (R-isomer) 5.6 μM	0.09	0.003	0.03
Verapamil (S-isomer) 5.6 μM	0.08	0.004	0.05
Quinidine SO_4 (1.3 mM)	0.08	0.83	10.4
Quinine SO_4 (13 mM)	0.08	0.83	10.4
Miscellaneous:			
Cyclosporin A (0.83 μM)	0.08	0.096	1.2
(4.2 μM)	0.08	0.012	0.15
Chloroquine (10 μM)	0.08	0.84	10.5

[a] Continuous drug exposure (approximately 5–6 days) using the MTT dye-reduction assay [9]

[b] These IC_{50} values represent the concentrations of MMC required to reduce cell growth an additional 50% beyond the reduction obtained using the modulator

[c] Defined as the ratio of the mitomycin C IC_{50} in resistant cells divided by that in sensitive cells

Table 3. Reversal of collateral doxorubicin resistance in parental and MMC-resistant L-1210 cells[a]

Modulator	Concentration (μM)	50% Inhibitory doxorubicin concentrations (μM)[b]		
		L-1210 cells	RL-1210/.1 cells	Relative resistance
None	–	0.029	0.69	24
Quinine HCl	31	0.0086	0.52	60[c]
Quinidine SO_4	31	0.01	0.52	52[c]
Verapamil (racemic)	25	0.0058	0.017	2.9[c]

[a] 6-Day MTT assays, both drugs present continuously

[b] Defined as the ratio of the doxorubicin IC_{50} in resistant cells divided by that in sensitive cells

[c] Ratios affected by *increased* sensitivity of parental L-1210 cells to doxorubicin when the modulator was added

MMC resistance-modulation studies

Agents selectively active against RL-1210/.1 cells were evaluated for their ability to reverse or modulate MMC resistance in vitro. Table 2 shows that the R- and S-isomers of verapamil produced the greatest magnitude of reversal of MMC resistance in RL-1210/.1 cells. The surfactant polysorbate 80 (Tween-80) was also effective at reversing MMC resistance. However, to achieve this effect, the surfactant had to be present at a concentration of 0.01% (vol/vol); this concentration also produced significant nonselective cytotoxicity when polysorbate was used alone (see Table 1).

The corticosteroids testosterone, estradiol, and hydrocortisone were not effective at reversing MMC resistance. In contrast, when added at its IC_{50} concentration, progesterone produced a concentration-dependent reversal of resistance (Table 2). The relative resistance factor for the combination of progesterone and MMC was 2.6.

The results in Table 3 show that neither quinine, quinidine, nor chloroquine could reverse MMC resistance in vitro. In contrast, these agents did sensitize the parental (non-MDR) L-1210 cells to doxorubicin (Table 3). The mechanism and significance of this unexpected finding are not known.

Discussion

Cross-resistance between MMC and DNA-intercalating agents is not a new observation. In 1970, 3-fold resistance to MMC was described in Chinese hamster ovary cells selected for 2,500-fold resistance to dactinomycin [3]. Interestingly, these cells became collaterally (more) sensitive to hydrocortisone, 6-mercaptopurine, and nitrogen mustard. Likewise, Matsumoto et al. [18] have used MMC to develop an L-1210 cell line that showed 14-fold resistance to MMC and 11-fold resistance to doxorubicin. Rose et al. [23] have also described cross-resistance to natural-product anticancer agents, including doxorubicin and vinca alkaloids, in a P-388 leukemia cell line developed for MMC resistance in vivo. Mizuno et al. have also observed cross resistance with doxorubicin in human ovarian cancer cells in vitro [19].

MMC is an atypical alkylating agent in that it is a natural product that contains aziridine and carbamate functional groups as the active alkylating moieties [27]. The mitosene-based structure of this natural product also differs significantly from the structure of most other alkylating agents. Indeed, the mitosene portion of the MMC molecule has been structurally compared with pyrrolizidine alkaloids that can cause outbreaks of hepatotoxicity following inadvertent ingestion by cattle [8]. Pyrrolizidines are plant alkaloids whose mechanism of toxicity involves DNA alkylation [8]. This suggests that the heightened expression of P-glycoprotein following MMC exposure in tumor cells could relate to the drug's structural similarity to a natural environmental feed toxin against which mammalian cells may have retained an adaptive means of protection.

A new observation is that the P-glycoprotein expressed following MMC exposure may be functionally distinct from that produced following doxorubicin exposure [2]. This is indicated by the finding that the cross-resistance to doxorubicin in RL-1210/.1 cells is not reversed by lysosomotropic amines such as quinine and quinidine. In contrast, these same cinchona alkaloids are highly effective at reversing doxorubicin-induced P-glycoprotein-mediated MDR in other human tumor cells [25]. Indeed, quinidine and quinine produced an unusual pattern of anticancer drug modulation in MMC-resistant cells: the MDR cells were largely unaffected, whereas parental cells became more sensitive to doxorubicin but not to MMC. Importantly, the results in Table 3 confirm that verapamil, which can also

concentrate in lysosomes [1], is active with doxorubicin [14, 22] and is consistently effective at modulating resistance to both mitomycin C and doxorubicin in RL-1210/.1 cells.

The reason for the highly selective cytotoxicity and the MDR-modulating activity of progesterone on MMC resistance may relate to progesterone-induced displacement of MMC binding to P-glycoprotein. A similar effect has been documented for progesterone in vinblastine-resistant J7.V1-1 mouse macrophage cells [30]. Progesterone also blocks azidopine photoaffinity labeling of cell membrances from the endometrium of the gravid uterus in the mouse [30]. This suggests that progesterone could be a natural (endogenous) substrate for the MDR_1 gene product in normal endothelial cells that have endocrine-secretory activities. It is unlikely that this phenomena can be explained by the presence of progesterone receptors in RL-1210/.1 cells, although this is currently being evaluated in our laboratory. Furthermore, the progesterone effect also does not appear to involve a collateral interaction with other corticosteroid receptors, since none of the other glucocorticosteroids or sex hormones tested produced similar effects in resistant cells (current results; [30]).

The MDR-modulating activity and selective cytotoxicity of progesterone seen in the current study required a high concentration of drug. However, the additive cytotoxicity may explain the positive results reported in a prior clinical trial using MMC and the synthetic progestin megestrol acetate in patients with refractory breast cancer [5]. Although P-glycoprotein was not measured in breast tumors in the earlier clinical trial, two new series have described elevations in P-glycoprotein content for breast-tumor specimens obtained from patients relapsing after primary drug treatment [13, 24]. In one of these studies, P-glycoprotein was detected in 4/8 specimens (50%) from untreated patients and in 4/5 specimens (80%) from patients previously treated with chemotherapy [24]. The latter study also showed that none of the P-glycoprotein-positive breast cancers from previously treated patients were sensitive to doxorubicin; in contrast, 6/8 breast tumors from untreated patients were sensitive to doxorubicin in vitro [24].

In addition to progesterone, verapamil also reversed MMC resistance in RL-1210/.1 cells. Both isomers of verapamil were equipotent in this activity, which required concentrations of only 5.6 μM (2.7 μg/ml, Table 2). This level is within the range of clinically achievable verapamil concentrations and thus may be clinically relevant [4, 10]. In this regard, it should be pointed out that the R-isomer of verapamil has less than one-tenth of the cardiovascular activity and toxicity of the S-isomer [28]. Thus, the use of R-verapamil to reverse MMC resistance in vivo is theoretically attractive, since it could possibly attain high serum concentrations without the significant cardiovascular toxicities associated with use of the commercial racemic mixture [9, 21]. Other preliminary reports have also shown that the R-isomer of verapamil can effectively reverse doxorubicin-induced MDR in vitro [16].

New studies are now being aimed at the examination of tumors from patients treated with MMC to look for enhanced P-glycoprotein expression. Moreover, the addition of high-dose progestins such as megestrol acetate to MMC-containing regimens is being evaluated in an attempt to overcome MMC resistance in such tumors.

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