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Phase I study of mitomycin C and menadione in advanced solid tumors

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Abstract A phase I study of mitomycin C with menadione (2-methyl-1,4-naphthoquinone, a vitamin K analogue which lowers intracellular pools of reduced glutathione) was designed as an approach to overcoming tumor cell resistance to alkylating agent chemotherapy. Patients with refractory solid tumors ($n = 51$) were treated with a 48-h continuous intravenous infusion of menadione followed by a bolus intravenous dose of mitomycin C at the completion of the menadione infusion. Initial menadione doses of 8.0 and 4.0 g/m^2 over 48 h were associated with hemolysis, so subsequent dose levels of menadione ranged from 1.0 to 3.0 g/m^2 with mitomycin C from 5 to 20 mg/m^2. All three patients treated with menadione at 8.0 g/m^2 and the single patient treated at 4.0 g/m^2 with mitomycin C at 5 mg/m^2 developed clinically significant hemolysis despite the presence of red blood cell glucose-6-phosphate dehydrogenase. Subsequently, a revised escalation scheme for menadione was used, and all patients tolerated menadione doses of 1–2.5 g/m^2 over 48 h with mitomycin C doses up to 20 mg/m^2. Since the 3.0 g/m^2 dose of menadione was associated with mild hemolysis in three of four patients, the maximum tolerated dose of menadione was established at 2.5 g/m^2. All of the mitomycin dose levels were tolerated without unexpected toxicities attributable to the combination. Prolonged infusions of menadione at doses which have been associated with lowering of intracellular glutathione pools in short-term exposure are limited by dose-dependent hemolysis, probably due to depletion of erythrocyte glutathione by menadione-related redox cycling. There was no detectable deleterious effect of pre-exposure to menadione on mitomycin C tolerance. We recommend a combination of menadione at 2.5 g/m^2 as a continuous intravenous infusion and mitomycin C at 15 mg/m^2 for further study in solid tumors for which treatment with single-agent mitomycin C is appropriate.

Key words. Mitomycin C · Menadione · Phase I studies

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Introduction

Mitomycin C is an antitumor quinone antibiotic which is metabolized via NADH and NADPH-dependent pyridine nucleotide dehydrogenases to intermediates which alkylate and crosslink DNA [10]. Treatment of malignant cells with mitomycin C also results in the formation of reactive oxygen species, which also contributes to its cytotoxicity [8, 11, 17]. One mechanism of resistance is increased drug detoxification of the chemotherapeutic agent by enzymes such as glutathione-*S*-transferase species which conjugate reactive alkylating intermediates with glutathione (GSH), yielding noncytotoxic aqueous metabolites [10].

Menadione (2-methyl-1,4-naphthoquinone), vitamin K_3, does not participate as a cofactor in the synthesis of coagulation proteins or possess anticoagulant properties. It is cytotoxic to both murine and human tumor cells, and a correlation exists between the degree of cytotoxicity and the depletion of intracellular glutathione pools [1]. Menadione has also been shown to reverse alkylator resistance in tumor cell lines in vitro, a property which may be related to its ability to deplete cellular glutathione pools [5].

Recent clinical studies have demonstrated that menadiol sodium diphosphate, which is converted in vivo to menadione, can be administered safely without significant toxicity at doses that achieve plasma concentrations in the 10^{-6} M range [2], a level which is

Table 1 Dose-escalation scheme

Level[a]	Menadione (g/m^2 over 48 h)	Mitomycin C (mg/m^2)	Number of patients starting at dose level	Number of cycles given at dose level
1	8	5	3	4
2	4	5	1	1
3	1	5	5	5
4	1.5	5	6	6
5A	2.0	5	11	15
6	3.0	5	4	4
5B	2.0	10	4	5
5C	2.0	15	4	6
5D	2.0	20	5	9
7	2.5	15	6	11

[a]Dose levels of menadione correspond with the numbers; dose levels of mitomycin C are designated by letters. The levels are listed in the order in which patient cohorts were studied

associated with antitumor cytotoxicity when maintained over a prolonged exposure time (96 h) [18]. Mitomycin is a component of numerous chemotherapy combinations for the treatment of advanced solid tumors (particularly non-small-cell lung cancers and gastrointestinal malignancies), and it is also used frequently in patients who have failed first-line therapy for several tumor types, particularly gastrointestinal and breast cancer.

Based on the finding of in vitro synergistic cytotoxicity between menadione and the quinone antitumor antibiotics [16], we designed this clinical phase I protocol to evaluate the safety and tolerability of a combination of menadione given as a continuous intravenous infusion prior to a single dose of mitomycin in patients with advanced solid tumors. Su et al. have reported that the optimal modulation of mitomycin cytotoxicity is achieved with a 48-h exposure to menadione (at least 50 μg-h/ml) [18]. Our phase I study demonstrated the safety of 4-h infusions of menadione at doses as high as 1360 mg/m^2 [2]. Therefore, we sought to evaluate the safety of menadione administered as a 48-h continuous intravenous infusion, starting at 8 g/m^2, to be followed by an intravenous bolus dose of mitomycin C.

Patients and methods

Patients

A total of 51 adult patients were enrolled in this study, which required the following eligibility criteria to be met prior to study registration: advanced cancer not previously treated with mitomycin C; Karnofsky performance status at least 60% and estimated survival at least 3 months; serum creatinine $\leq$ 1.5 mg/dl or clearance $\geq$ 60 ml/min, hemoglobin $\geq$ 10 g/dl, white blood cell count $\geq$ 4000/μl, platelets $\geq$ 150 000/μl, serum alanine aminotransferase and aspartate aminotransferase both $\leq$ 80 units/ml, bilirubin $\leq$ 1.2 mg/dl, prothrombin time within 1 s of the control value; at least 4 weeks beyond any prior chemotherapy or radiotherapy; positive erythrocyte glucose-6-phosphate dehydrogenase by spot test; and the ability to provide voluntary, written informed consent. This study was approved by the City of Hope Institutional Review Board.

Required prestudy testing consisted of complete blood count with reticulocyte count, 18-function biochemistry panel, prothrombin time, and a radionuclide-gated blood pool scan for estimation of the left ventricular ejection fraction. During the course of treatment, blood counts and chemistries were monitored weekly, and radionuclide left ventricular ejection fraction was to be repeated 6 weeks following the last mitomycin C exposure.

Therapy protocol

Menadiol sodium diphosphate (Synkayvite; Hoffman-LaRoche, Nutley, N.J.) was administered to inpatients as a 48-h continuous intravenous infusion followed immediately by a rapid intravenous infusion of mitomycin C (Bristol-Myers, Wallingford, Ct.). The initial doses and the revised dose-escalation scheme are shown in Table 1. The reason for the changes in the starting menadiol dose and the duration of the continuous intravenous infusion are provided in the results section. Treatment was repeated at 4-week intervals and required recovery of any toxicity to $\leq$ grade 1 and no evidence of tumor progression.

Results

Of 51 patients entered into the study, 49 were evaluable for toxicity. One patient was ineligible because of an on-study bilirubin of 2.3 mg/dl, and one patient was inevaluable because of the erroneous omission of mitomycin C from the regimen. The demographic features of the eligible patient population are listed in Table 2. Most patients had advanced cancer of the aerodigestive organs and were of advanced age with moderately compromised performance status. All patients had a positive spot test for the presence of erythrocyte glucose-6-phosphate dehydrogenase, and 36 patients had received one or more chemotherapy regimens for advanced disease, predominantly cisplatin-containing combinations or modulated 5-fluorouracil.

Patient tolerance of the menadiol infusion was excellent, with no significant nausea, emesis, or other adverse reactions during the treatment period. Mitomycin was also tolerated without any unusually severe adverse effects attributable to the modulation by menadione. Grade 3 neutropenia was observed in one of nine cycles at 2 g/m^2 menadiol with 20 mg/m^2 mitomycin C (level 5D, Table 1) and one of six cycles at

Table 2 Demographic data

Age (years; median, range)	61 (25–76)
Karnofsky status (%; median, range)	80 (60–100)
Males/females	20/30
Tumor type	
Lung - squamous or adenocarcinoma	16
small cell	1
Head and neck - squamous	6
Gastrointestinal adenocarcinoma	14
Unknown primary adenocarcinoma	3
Ovary	1
Cervix - squamous	1
Endometrial	1
Breast	2
Kidney	2
Melanoma	2
Bone sarcoma	1
Prior chemotherapy	
Cisplatin combinations	19
5-FU combinations	22
Adriamycin combinations	8
Total eligible patients	50

2 g/m^2 menadiol with 15 mg/m^2 mitomycin C (level 5C). Grade 4 neutropenia was observed in one treatment cycle at level 5D. Grade 3 thrombocytopenia was observed in two cycles at level 5C. No clinical cardiotoxicity was observed; the mean left ventricular ejection fraction pretreatment was 62% (range 50–73%), and the mean post-treatment ejection fraction in the 19 patients reevaluated was 60% (range 47–71%).

Distinct criteria for defining hemolysis separately from the common toxicity grading criteria for anemia were not addressed at the outset of the study, because we did not anticipate this complication. We observed clinically significant abrupt drops in the hemoglobin level in all of the three patients treated at the original starting menadiol dose of 8 g/m^2 over 48 h and in the single patient treated at 4 g/m^2. The early onset of severe anemia with no evidence of bleeding was not consistent with myelosuppressive chemotherapy and was accompanied by variable other laboratory perturbations (serum haptoglobin, bilirubin, and lactate dehydrogenase (LDH) and urine hemosiderin) supportive of a diagnosis of hemolysis (Table 3). We therefore revised the menadiol escalation scheme, as illustrated in Table 1 which shows the total number of patients and treatment cycles given at each of the dose levels on the revised escalation scheme. Our subsequent definition of hemolysis was based on the observation of an abrupt fall in hemoglobin of at least 2 g/dl with no evidence of bleeding, a variable elevation of bilirubin, and a variable reticulocyte response which could have been blunted by the myelosuppressive effects of the mitomycin C. Serum LDH levels were inconsistently elevated, often attributable to tumor, and not useful in confirming the diagnosis.

There was no evidence of microangiopathic changes on peripheral blood smears, nor was there any evidence of renal insufficiency or severe thrombocytopenia suggestive of the mitomycin-associated microangiopathic hemolytic-uremic syndrome [13]. Among five cycles

Table 3 Data from patients who showed evidence of hemolysis (*DOD* "dead of disease" – death due to progressive tumor

Patient number	Dose level	Pretreatment Hb (g/dl)	Nadir Hb (g/dl)	Days after start of treatment	Pretreatment TBili (mg/dl)	Max TBili (mg/ml)	Outcome
1	1- cycle 1	15.4	(No change)	–	0.4	2.4*	
1	1- *cycle* 2	12.5	9.4	5	0.4	4.3	Unknown – DOD at 3 months
2	1	12.2	7.3	18	0.4	1.5	Full recovery
3	1	13.3	6.2	14	0.6	1.7	Full recovery
4	2	11.5	8.4	14	0.3	0.3	Full recovery
28	6- cycle 1	17.0	13.8	13	0.9	2.0	Full recovery; no evidence of hemolysis on retreatment at dose level 5A
28	5A- cycle 2	15.9	(No change)	–	–	–	
29	6	10.8	8.0	7	0.4	1.1	Continued stable anemia, DOD within 8 wks
31	6- cycle 1	10.9	7.8	4	0.5	1.0	Full recovery: stable throughout 3 more treatments at dose level 5A and 1 treatment at 5B
31	5A- cycle 2	10.1	8.3	14			
31	5A- cycle 3	9.6	(Transfused intermittently)	–			
31	5B- cycle 4	8.6					
38	5C	10.1	6.8	–	0.3	0.4	DOD 17 days after start of treatment
46	7	11.2	(Slow steady fall)	8	0.3	0.3	Stable anemia required approximately 1 unit RBC transfusion per month
46	7	8.6	7.5	–	0.2	0.3	DOD at 2 months

*hemolyzed specimen not redrawn

given to five patients at 1.0 g/m^2 menadiol, six cycles given to six patients at 1.5 g/m^2, and 15 cycles given to 11 patients at 2.0 g/m^2 (levels 3, 4 and 5A), all with the lowest mitomycin C dose (5 mg/m^2), there were no episodes of hemolysis. When the 2 g/m^2 menadiol dose was combined with the 10, 15 and 20 mg/m^2 doses of mitomycin C (levels 5B, 5C and 5D), no episode of hemolysis was observed among five cycles in four patients, six cycles in four patients, and nine cycles in five patients, respectively. Hemolysis was again observed in three of the four patients starting therapy at 3.0 gm/m^2 menadiol with 5 mg/m^2 mitomycin C but did not recur upon retreatment at the 2 g/m^2 menadiol dose (one patient receiving one additional cycle and one patient receiving three additional cycles).

The final dose of menadiol studied was thus halfway between the consistently safe dose of 2 g/m^2 and the 3 g/m^2 dose which had caused hemolysis in three of four patients. Six patients received a total of 11 treatment cycles consisting of 2.5 g/m^2 menadiol and 15 mg/m^2 mitomycin C, and no hemolysis occurred. Table 3 contains the detailed data from the patients who were judged to have evidence of hemolysis attributable to protocol treatment. Although two of the ten patients described in this table did not qualify by a full 2.0 g/dl fall in hemoglobin, the rest of their clinical and laboratory data were felt to support the diagnosis of hemolysis.

In this group of mainly pretreated patients with highly drug-resistant tumor histologies, no objective antitumor responses were observed. However, in order to further explore the potential activity of this form of chemomodulation in selected tumor types, we recommend the use of the 2.5 g/m^2 dose for further evaluation in phase II trials.

Discussion

The present trial was based on preclinical data suggesting the possibility of overcoming resistance to the quinone antibiotic mitomycin C by decreasing intracellular GSH levels. The mechanisms by which menadione lowers GSH pools include the production of reactive oxygen species by menadione redox cycling and the covalent binding of drug to GSH [7]. The potential for synergism of menadione with other anticancer drugs has been shown in a variety of in vitro systems. At levels which are several-fold lower than those required for direct in vitro cytotoxicity, pretreatment of some tumor cell lines with menadione has been shown to synergize with doxorubicin and mitomycin-C, reducing their IC_{50} values (concentration at which half of the cells are growth-inhibited) by 10- to 50-fold from the IC_{50} value of the single agent (J. Doroshow, unpublished observations).

This effect of menadione pretreatment is directly related to its ability to deplete intracellular reduced glutathione. Further, the introduction of the enzyme glutathione-*S*-transferase directly into a human breast cancer cell line by mechanical disruption of the cell membrane has been shown to confer resistance to several antitumor quinone antibiotics (doxorubicin, daunorubicin, mitomycin C) as well as menadione in proportion to the quantity of intracellular enzyme activity achieved [9]. The possible mechanisms for the apparent drug resistance of tumor cells which express increased levels of GSH include enhanced inactivation of the drug by conjugation to GSH and detoxifying products of redox cycling of the quinone moiety, e.g. hydrogen peroxide, or scavenging other byproducts of the free radical metabolism of the quinone antibiotic, such as reactive organic peroxides.

Recently, the effect of buthionine sulfoximine (BSO) and ethacrynic acid (EA), a glutathione transferase inhibitor, on the cytotoxic activity of mitomycin C has been studied in the P388 mouse leukemia cell line as well as in a multidrug-resistant variant (P388/R-84) that was cross-resistant to mitomycin C. Xu and Singh found that depletion of GSH by BSO or inhibition of glutathione transferase by EA results in enhancement of mitomycin C cytotoxicity in P388/R84 cells. BSO also enhanced the cytotoxicity of two mitomycin C analogues in these cells [19].

Previous studies have demonstrated that menadione itself possesses some antitumor activity in the absence of other drugs. The earlier investigations of other vitamin K analogues were generally not pursued because of the unacceptable interactions of these drugs with the coagulation system [5]. However, menadiol sodium diphosphate, which does not affect the coagulation cascade, is cytotoxic against a broad spectrum of fresh human tumors as well as the murine leukemia cell line L1210 and the murine hepatoma line HII4E in the soft agar clonogenic system [6].

Early clinical investigations based on the combination of vitamin K analogues and chemotherapeutic agents confirmed the feasibility of administering selected combinations to patients [4, 14]. In a phase II study of patients with metastatic colorectal cancer, menadiol was given at 20 mg/m^2 every 6 h by intramuscular injection for 120 h with Coumadin 5 mg orally each day for 5 days and 5-fluorouracil 20 mg/kg per day as a 120-h continuous intravenous infusion. The toxicity of this regimen was not different than that associated with a 5-day continuous infusion of 5-FU alone at the same dose. Plasma levels of vitamin K_3 in the micromolar range, which is known to be synergistic with dicumarol, were achieved by this schedule, and clinical antitumor activity was observed in 4 of 15 patients with metastatic colorectal cancer [4]. Nagourney et al. treated seven patients with solid tumors or hematologic malignancies with combinations of chemotherapeutic agents and menadiol at varying doses. No significant enhancement of the expected

chemotherapy side effects was observed at the highest dose of menadiol tested (3200 mg/m^2) [14].

In our initial phase I trial of menadiol alone, patients were able to tolerate dose levels from 40 to 1360 mg/m^2 with no clinical or laboratory toxicities when the drug was administered as a rapid intravenous bolus infusion over 30–300 min. Symptoms of transient perioral paresthesiae and dyspepsia which occurred at the highest dose levels were attributed to the sodium metabisulfite preservative. These symptoms were ameliorated by prolonging the infusion time. Patients treated at this dose level achieved plasma menadione levels in the 10^{-6} M range lasting 4–6 h after the completion of a dose [2].

Pharmacokinetic analysis was not performed in the present study, but the initial doses and duration of menadiol infusion were selected on the basis of our previous experience and the expectation that optimal modulation of the antitumor effect of mitomycin C would require a more prolonged exposure of the tumor to menadione. Thus, we proposed a 48-h initial infusion, using 8 g/m^2 of menadiol, and subsequent dose levels were projected to include both a dose escalation and a more prolonged duration of infusion. However, the observation of severe hemolysis at the first dose level and again at 50% of the starting menadiol dose over the same infusion period led us to conclude that erythrocyte glutathione pools might be lowered significantly by this treatment, which led to a potential flux of menadione-induced reactive oxygen metabolism that could have produced excess oxidative stress even in the presence of the enzyme glucose-6-phosphate dehydrogenase.

The role of mitomycin C in the production of hemolysis in this treatment program is unclear. Although mitomycin C has frequently been associated with a microangiopathic hemolytic anemia, which appears to be related to the cumulative dose administered, the patients described on the initial dose levels in this study received very small doses of mitomycin C. Furthermore, there was no evidence of microangiopathic changes in the peripheral blood smear, nor was there any evidence of renal insufficiency or severe thrombocytopenia which often accompany this hemolyticuremic-like syndrome. In a parallel study performed at our institution using cyclophosphamide as the alkylator in combination with menadiol, we observed no hemolysis in any of the five patients treated with 8 g/m^2 of menadione, but based on the severe episodes observed in the current study, we also revised the menadiol levels and length of infusion of menadiol in the parallel trial.

Other agents which have been used with a similar rationale include BSO, a drug which is known to inhibit gamma-glutamyl-cysteine synthase. Based on in vitro data demonstrating the sensitizing effects of BSO on cell lines and in animal models treated with alkylating agents or platinum analogues, O'Dwyer et al. studied combinations of BSO and L-phenylalanine mustard (L-PAM) in patients with advanced malignancies, the majority of whom had heavily pretreated, alkylator-resistant ovarian cancer [15]. Despite the achievement of marked depletion of peripheral blood mononuclear cell GSH to levels in the range associated with in vitro sensitization to alkylators, tumor GSH levels (measured in patients with tumor accessible for serial biopsies) were only inconsistently and incompletely depleted. No overt evidence of hemolysis was observed by routine laboratory testing. These investigators recommended a 1–3 day phase of pretreatment with BSO followed by the therapeutic alkylating agent.

Bailey et al. recently reported a phase I trial of BSO and L-PAM in which patients also received a cycle of L-PAM alone [3]. Using BSO doses one to eight times those used by O'Dwyer et al. these investigators found moderate depletion of glutathione levels in peripheral blood mononuclear cells of patients receiving BSO, but the effect was transient, incomplete (minimum GSH levels achieved in peripheral blood mononuclear cells, and in one patient's ascites, 30–40% of baseline), and not well correlated with the BSO dose. Although the modulator was nontoxic and did not appear to add significantly to the toxicities of L-PAM, the authors concluded that the desired degree of intracellular GSH depletion had not been achieved by this regimen and therefore did not recommend further use of this schedule.

Attempts to biochemically modulate the intracellular effects of the quinone antibiotic drugs and alkylating agents using GSH-depleting agents such as menadione and BSO have been limited so far by the incomplete and sometimes paradoxical effects of these agents, which may have opposing effects on the cytotoxicity of certain chemotherapeutic agents depending on the dose and intracellular drug levels achieved. For example, Keizer et al., utilizing the human lung cancer line SW1573, have shown that menadione at a concentration of 2.7 μM can protect cells against in vitro cytotoxicity from a range of concentrations of mitomycin C. This effect was attributed to the function of menadione as an artificial electron acceptor competing for electrons required for the reductive activation of mitomycin C to the cytotoxic bifunctional alkylating agent by cellular flavoproteins [12]. It is likely that future studies will need to combine agents which modulate more than one of the mechanisms of cellular resistance to the chemotherapeutic agent of interest (analogous to combination chemotherapy itself) in order to achieve maximum therapeutic activity with a tolerable spectrum of toxicities.

References

1. Akman SA, Doroshow JH, Dietrich MF, Chlebowski RT, Block JS (1987) Synergistic cytotoxicity between menadione and

dicumarol vs. murine leukemia L1210. J Pharmacol Exp Ther 240: 486
2. Akman S, Carr B, Leong L, Margolin K, Odujinrin O, Doroshow J (1988) Phase I trial of menadiol sodium diphosphate (SYNKAVITE®) (M) in advanced cancer. Proc Am Soc Clin Oncol 7: 76
3. Bailey HH, Mulcahy RT, Tutsch KD, Arzoomanian RZ, Alberti D, Tombes MG, Wilding G, Pomplun M, Spriggs DR (1994) Phase I clinical trial of intravenous L-buthionine sulfoximine and melphalan: an attempt at modulation of glutathione. J Clin Oncol 12: 194
4. Chlebowski RT, Block JB, Dietrich M, Octay E, Barth N, Yanagihara R, Gota C, Ali I (1983) Inhibition of human tumor growth and DNA biosynthetic activity by vitamin K and warfarin in vitro and clinical results. Proc Am Assoc Cancer Res 24:653
5. Chlebowski RT, Akman SA, Block JB (1985) Vitamin K in the treatment of cancer. Cancer Treat Rev 12: 49
6. Chlebowski RT, Dietrich M, Akman S, Block JB (1985) Vitamin K_3 inhibition of malignant murine cell growth and human tumor colony formation. Cancer Treat Rep 69: 527
7. Di Monte D, Ross D, Bellomo G, Eklöw L, Orrenius S (1984) Alterations in intracellular thiol homeostasis during the metabolism of menadione by isolated rat hepatocytes. Arch Biochem Biophys 235: 334
8. Doroshow JH (1986) Role of hydrogen peroxide and hydroxyl radical formation in the killing of Ehrlich tumor cells by anticancer quinones. Proc Natl Acad Sci USA 83: 4514
9. Doroshow J, Burke T (1988) Resistance to anticancer quinone-induced cytotoxicity produced by introduction of glutathione-S-transferase (GST) into human MCF-7 breast cancer cells. Proc Am Assoc Cancer Res 29: 271
10. Dorr RT (1988) New findings in the pharmacokinetic, metabolic, and drug-resistance aspects of mitomycin C. Semin Oncol 15: 32
11. Dusre L, Rajagopalan S, Eliot HM, Covey JM, Sinha BK (1990) DNA interstrand cross-link and free radical formation in a human multidrug-resistant cell line from mitomycin C and its analogues. Cancer Res 50: 648
12. Keizer H, De Leeuw SJ, Van Rijn J, Pinedo HM, Joenje H (1989) Effect of artificial electron acceptors on the cytotoxicity of mitomycin C and doxorubicin in human lung tumor cells. Eur J Cancer Clin Oncol 25: 1113
13. Lesesne B, Rothschild N, Erickson B, Korec S, Sisk R, Keller J, Arbus M, Woolley PV, Chiazze L, Schein PS, Neefe JR (1989) Cancer-associated hemolytic-uremic syndrome: analysis of 85 cases from a national registry. Clin Oncol 7: 781
14. Nagourney R, Weisenthal L, Dill P, Just R, Fass L, Baker J (1987) Menadiol in combination with cytotoxic chemotherapies; the feasibility for resistance modification in human cancers: a pilot study. Proc Am Soc Clin Oncol 6: 35
15. O'Dwyer PJ, Hamilton TC, Young RC, LaCreta FP, Carp N, Tewk KD, Padavic K, Comis RL, Ozols RF (1991) Depletion of glutathione in normal and malignant human cells in vivo by buthionine sulfoximine: clinical and biochemical results. J Natl Cancer Inst 84: 264
16. Parekh HK, Mansuri-Torshizi H, Srivastava TS, Chitnis MP (1992) Circumvention of adriamycin resistance: effect of 2-methyl-1,4-naphthoquinone (vitamin K_3) on drug cytotoxicity in sensitive and MDR P388 leukemia cells. Cancer Lett 61: 147
17. Pritsos CA, Sartorelli AC (1986) Generation of reactive oxygen radicals through bioactivation of mitomycin antibiotics. Cancer Res 46: 3528
18. Su Y-Z, Duarte TE, Dill PL, Weisenthal LM (1987) Selective enhancement by menadiol of in vitro drug activity in human lymphatic neoplasms. Cancer Treat Rep 71: 619
19. Xu BH, Singh SV (1992) Effect of buthionine sulfoximine and ethacrynic acid on cytotoxic activity of mitomycin C analogues BMY 25282 and BMY 25067. Cancer Res 52: 6666