Cancer Chemother Pharmacol (1993) 32: 373–378

Cancer Chemotherapy and Pharmacology

Human autopsy-tissue distribution of menogaril and its metabolites

David J. Stewart [1, 2], **Darshan Grewaal**[1, 2], **Robert M. Green**[1], **Rakesh Goel**[1, 2], **Nadia Mikhael**[2], **Vital A. J. Montpetit**[2], **Deidre Redmond**[1], **Robert Earhart**[3]

[1] Ontario Cancer Treatment and Research Foundation, Ottawa Regional Cancer Centre, Ottawa, ON, Canada
[2] University of Ottawa Faculty of Medicine, Ottawa, ON, Canada,
[3] Upjohn Pharmaceutical Co., Kalamazoo, Michigan, USA

Received 4 December 1992/Accepted 12 March 1993

Abstract. Autopsy-tissues were obtained from eight patients who had last received menogaril (total cumulative dose, 175–1080 mg/m^2) intravenously (one patient) or orally (seven patients) from 1 to 285 days prior to death. Tissue samples were assayed for menogaril and its metabolities by high-pressure liquid chromatography. Unchanged menogaril was found only in a single lung-tissue sample from a patient who had died <24 h after receiving his last treatment. *N*-Demethylmenogaril was found in two lung-tissue samples and in single samples of the thyroid, lymph node, pancreas, cerebellum, and tumor. The major menogaril metabolite found in human autopsy-tissues was 7-deoxynogarol. The highest 7-deoxynogarol concentrations were found in the large bowel (median, 201 ng/g), liver (median, 183 ng/g), and lung (median, 177 ng/g). The heart ranked as the 9th of 18 organs in median 7-deoxynogarol concentration, after the large bowel, liver, lung, tumor, thyroid, skeletal muscle, adrenal gland, and kidney. The lowest concentrations were detected in brain tissue. Our results suggest that the low degree of cardiac toxicity and the possible pulmonary toxicity of menogaril may be related to relative tissue concentrations of menogaril metabolites. Tumor 7-deoxynogarol concentrations were comparable with those in normal tissues, except that concentrations in intracerebral tumors were higher than those in the normal brain. Tissue 7-deoxynogarol concentrations appeared to be directly related to the cumulative dose and inversely related to the time from the last treatment to death; the value obtained by dividing dose by time correlated (P <0.05) with tissue 7-deoxynogarol concentrations.

Correspondence to: D. J. Stewart, Professor of Medicine and Pharmacology, Head, Division of Medical Oncology, Ottawa Regional Cancer Centre, Civic Division, 190 Melrose Avenue, Ottawa, ON, Canada K1Y 4K7

Introduction

Menogaril is a new anthracycline derivative that is active orally [9]. It is also considerably less cardiotoxic in animals than is doxorubicin [9]. In clinical trials, menogaril has demonstrated activity against breast cancer when given both orally [24] and intravenously [5]. In addition, major responses have been seen in patients with carcinomas of the bladder and kidney and in gliomas [19, 21, 25].

Only minimal cardiotoxicity has been noted in clinical studies to date, and menogaril is less than 1/15th as potent a cardiotoxin as is doxorubicin in animal models [9]. Menogaril achieved a much higher area under the concentration-time curve in the lung and spleen than in the heart in rabbits [3]. In our early studies of intravenous menogaril, we noted that some patients developed cough and dyspnea on the administration of menogaril [19] and postulated that this might possibly be due to high drug concentrations being attained in human lung tissue, analogous to the situation in animals [3]. We have previously noted that cisplatin nephrotoxicity [16] and neurotoxicity [6] are related to tissue platinum concentrations, and we have also reported that the cardiotoxic drug mitoxantrone achieves higher relative concentrations in the heart (as compared with other tissues) than do most noncardiotoxic agents that we have studied [17]. In a small study involving patients treated with 4-(9-acridinylamino)-methanesulfon-*m*-aniside (m-AMSA), there was a suggestion that both neurotoxicity and cardiotoxicity might be related to tissue drug concentrations [14]. Finally, studies we have done with doxorubicin have indicated high cardiac concentrations of both doxorubicin and its toxic metabolite doxorubicinol [23], suggesting that this metabolite may play a role in the cardiotoxicity of doxorubicin.

We have completed a total of three phase I studies of menogaril (using varying routes and schedules) [19, 21, 25], and we have also participated in phase II studies of menogaril's activity in gliomas [26] and in advanced breast cancer [24]. During these studies of menogaril, we collected autopsy-tissue samples from eight

patients. In this paper, we report the concentrations of menogaril and its metabolites in human autopsy-tissues.

Materials and methods

Sample collection. Autopsy-tissue samples were collected from six men and two women who had received menogaril on a weekly schedule either intravenously (one patient) or orally (seven patients). The interval between the last treatment and death ranged from 1 to 285 days. Total cumulative lifetime menogaril doses varied from 175 to 1,080 mg/m^2. Following collection, the tissues were stored at –20°C until assayed.

Chemicals. Menogaril, *N*-demethylmenogaril, 7-deoxynogarol and the internal standard (7R)-*O*-ethylnogarol were kindly provided by Dr. J. P. McGovern (The Upjohn Company, Kalamazoo, Mich.). Methanol, acetonitrile [high-pressure liquid chromatography (HPLC) grade], formic acid (88%), ammonia solution (28%–30%), and silver nitrate were purchased from BDH Inc. (Toronto), and ammonium phosphate was obtained from J. T. Baker Chemical Co. (Phillipsburg, N.J.). All reagents were of analytical grade or of the highest purity available.

Sample extraction. Menogaril and its metabolites were estimated by HPLC using an adaptation of an assay we have previously used for anthracyclines [2, 10]. Stock solutions of menogaril and its related compounds (1 mg/ml) were prepared in 0.01 *M* HCl and stored in a dark environment at 4°C. Dilutions (10 and 1 μg/ml) were prepared with the mobile phase just before their use. Tissues were homogenized with a Brinkmann Polytron (setting 7–8) in 3 vol. (w/v) of 0.3 *M* ammonium phosphate buffer (pH 6.4). Aliquots (1 ml) in triplicate were pipeted into glass centrifuge tubes (Corex number 8441) containing 10 μl of a 10-μg/ml solution of the internal standard. Homogenized samples were stored in a dark environment at –20°C until analyzed (usually the next day). The samples were thawed and vortexed with the addition of 0.2 ml silver nitrate solution (33%, w/v) to extract drug from the DNA. At 10 min thereafter, the samples were vortexed (1 min) with methanol (3 ml) and left on ice. The samples were subsequently centrifuged at 11,000 rpm (10 min) in a TR/MN head in a Jouan MR14.11 refrigerated centrifuge. Supernatants were diluted to 30 ml with distilled water and passed under vacuum through C18 Bond-Elut columns (100 mg) secured in a Vac-Elut vacuum box fitted with 8-ml reservoirs. The columns had been preconditioned by washing with 0.25 *M* HCl in methanol (4 ml), methanol (4 ml), and water (25 ml). The columns were washed with 25 ml water and the compounds were eluted from the columns with 0.25 *M* HCl in methanol (0.3 ml). The residual eluent was forced out with nitrogen under pressure.

HPLC assay. Aliquots of 117 μl eluate were pipeted into MicroSun inserts (number 1190), which were placed in autosampler vials, and 75 μl was analyzed with a Shimadzu HPLC consisting of an SLC-6A system controller, an SIL-6A autoinjector, an LC-6A pump, an RF-535 fluorescence HPLC monitor, and a C-R5A integrator recorder. The compounds were separated at a flow rate of 1.5 ml/min on a Waters μBondapak phenyl column (300 × 3.9 mm) equipped with a Guard-Pak Resolve CN guard column and were detected by fluorescence (470-nm excitation and 550-nm emission). The mobile phase consisted of acetonitrile:0.4 *M* ammonium formate buffer (pH 4.0; 25:75, v/v). Menogaril and its metabolites were identified by retention time and were quantitated by comparison of the peak height of a sample with standard curves constructed for that compound by adding known amounts of the compound to homogenized control human autopsy tissues. All of the data points weighted with the reciprocal of concentration were used in constructing regression curves. Average recovery of the compounds from homogenized control human autopsy tissues was over 90%, and the limit of quantitation was 15 ng/g tissue. There was no observed decomposition of standards stored in a dark environment at 4°C over a period of 60 days.

Table 1. Concentration of *N*-demethylmenogaril in autopsy tissues from patients who had received menogaril antemortem[a]

	Patient number		
	1	3	6
Cumulative menogaril (mg/m^2)	175	720	460
Menogaril route	oral	oral	i. v.
Time (days)[b]	1	13	57
Tissue *N*-demethylmenogaril (ng/g):			
Lung	532	213	
Thyroid	975		
Lymph node			15
Pancreas			93
Brain			14
Glioma			11

[a] Of 120 tissues assayed (see Table 2), no other tested tissues had any detectable *N*-demethylmenogaril. Values below the level of quantitation must be interpreted cautiously

[b] Time from the last menogaril treatment to death

Results

Menogaril was detected in only 1 of the 120 tissue samples assayed, namely, lung tissue from a patient who had died <24 h after receiving the drug orally. The menogaril concentration in this tissue was 69 ng/g.

The metabolite *N*-demethylmenogaril was detected in only 7 tissue samples, including 2 lung samples (Table 1). Comparison of the data obtained from patient 6 with those gathered from other patients suggests that there may be more *N*-demethylmenogaril in tissue after i.v. treatment with menogaril than after oral administration, although the data are too limited to permit firm conclusions to be drawn.

7-Deoxynogarol was the major menogaril metabolite detected in autopsy-tissues. Although tissue concentrations of 7-deoxynogarol were quite variable (Table 2), they generally tended to increase with higher cumulative menogaril doses and to decrease with increasing time from the last treatment to death. According to Spearman rank-order correlation coefficients, tissue concentrations of 7-deoxynogarol in both normal tissues and tumor correlated significantly ($P < 0.05$) with the value obtained by dividing the total cumulative menogaril dose by the time from the last treatment to death (Table 3). Median 7-deoxynogarol concentrations in all nontumor or tumor tissues were calculated for each patient, and these median values were used for the statistical analyses.

7-Deoxynogarol reached its highest concentrations in the large bowel, liver, and lung (Fig. 1). Only very low concentrations were found in normal brain or testicle tissue. The heart ranked as the 9th of 18 evaluable tissue types with respect to median 7-deoxynogarol concentrations. We could not directly correlate menogaril toxicity with organ concentrations in this study since patient numbers were small, the drug dose and the time from the last treatment varied widely, and none of these particular patients exhibited any visceral toxicity from menogaril.

Table 2. Concentrations of 7-deoxynogarol in autopsy tissues from patients who had received menogaril at some time antemortem[a]

	Patient number							
	1	2	3	4	5	6	7	8
Menogaril (mg/m²)[b]	175	675	720	1,080	325	460	1,898	900
Time[c]	1	3	13	27	39	57	142	285
Route	oral	oral	oral	oral	oral	i. v.	oral	oral
Tissue 7-deoxynogarol (ng/g):								
Median[d]	74	3,532	123	872	0	2	6	0
Adrenal	154			513	0	24		
Kidney	72	11,663	103	1,323	0	10		
Testicle	151	5,310			0	13		2
Lymph Node	24		499	1,312	0	2		
Liver	117	6,676	248	2,990	0	3		
Lung	143	9,080	211	1,090	0			0
Pancreas	72	6,896	154	1,287	0	7	7	
Thyroid	94		142	1,434	0			
Heart	88	2,930	308	671	0	0	23	
Prostate	76	1,300				2		
Spleen	70	4,096	144	114	0	0		0
Large Bowel	306	2,576	41	563	0	0		
Small Bowel	59	4,133	58	653	0	0		
Muscle		816	101	191	0			0
Stomach	37	1,836	63	444	0			0
Bladder	43	770	55		0	0	5	
Brain	2	221	14	62	0	0	4	0
Tumor: Liver			282		0			
Adrenal			243		0			
Prostate			193					
Brain	4					2		
Vagina				335				
Unknown		543						
Node	24							
Median	14	543	243	335		2		

[a] Values of <15 ng/g are below the limit of accurate quantitation and hence represent estimates. Where no value appears, no tissue was available for testing, since tissue samples had previously been utilized to assay other drugs that the patient had also received

[b] Cumulative lifetime dose

[c] Days from the last treatment to death

[d] Median tissue 7-deoxynogarol concentration for normal (nontumor) tissues

Table 3. Spearman rank-order correlation coefficients for median tissue 7-deoxynogarol concentrations versus the cumulative menogaril dose and the time from the last treatment to death

Variable	Normal tissues		Tumor	
	Coefficient	*P*	Coefficient	*P*
Dose	0.17	NS	0.66	<0.05
Time	–0.71	<0.05	–0.54	NS
Dose/time[a]	0.86	<0.05	0.71	<0.05

NS, Not significant

[a] Dose/time: the cumulative lifetime menogaril dose divided by the time in days from the last menogaril treatment to death

Tumor concentrations of 7-deoxynogarol were comparable with those in normal tissues (Fig. 1, Table 2). The concentrations of 7-deoxynogarol observed in intracerebral tumors appeared to be lower than those seen in extracerebral tumors, despite the failure to detect *N*-demethylmenogaril in any tumors except for a single intracerebral tumor (Table 1).

Discussion

Following administration of menogaril, the major drug species we found in human autopsy-tissues was 7-deoxynogarol. It is unclear from our data whether this finding might have been due to greater uptake or retention of this metabolite in tissues or to antemortem or post-mortem conversion of the parent drug and/or other metabolites to 7-deoxynogarol in tissues. That the only tissue sample containing the parent compound was obtained from a patient who had died <24 h after receiving menogaril suggests that the pattern seen is due either to antemortem efflux of menogaril from tissues or to antemortem conversion of menogaril to 7-deoxynogarol within tissues.

Menogaril may be converted to 7-deoxynogarol by xanthine oxidase [3]. The lack of detectable 7-deoxynogarol in human plasma, urine, and bile in other studies [4, 7, 27] is consistent with the conversion of menogaril to 7-deoxynogarol in tissues as opposed to the uptake of 7-deoxynogarol into tissues from plasma. In addition, only a small percentage of the total delivered dose of menogaril is subsequently

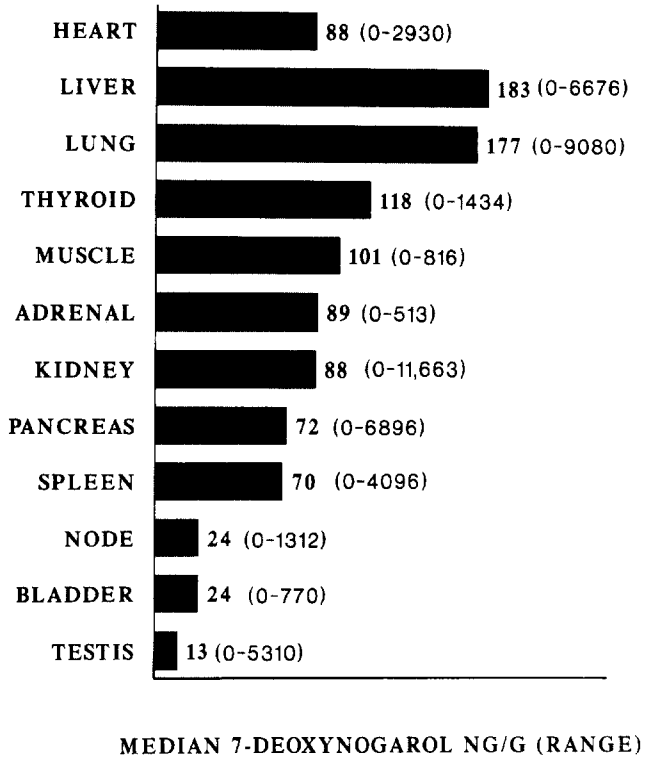

Fig. 1. Median concentrations of 7-deoxynogarol in human autopsy-tissues after antemortem treatment with menogaril. Values below 15 ng/g were below the limit of accurate quantitation and hence are only rough estimates that must be interpreted cautiously

found in human urine and bile in the form of menogaril or 7-demethylmenogaril [4, 27], suggesting that the drug either is excreted as nonfluorescent metabolites or is retained in tissues as the parent drug or as metabolites. In rabbits, the parent compound was the major tissue species detected at both 1 and 8 h, and 7-deoxynogarol was the major tissue *metabolite* found [3]. In rabbits, as in our patients, very little intact menogaril or *N*-demethylmenogaril was found in tissues after the first 24 h [3]. No information was provided on the organ concentrations of 7-deoxynogarol after the first 8-h period [3]. In any event, both the data in rabbits and our human data suggest that 7-deoxynogarol is an important tissue metabolite of menogaril, despite its not being prominent in biological fluids.

Although photodecomposition of menogaril may occur during sample handling [9], this would not explain our observations, since tissue samples spiked with menogaril and its metabolites were used to construct standard curves and were handled in exactly the same manner as the experimental samples. These showed no deterioration of menogaril or its metabolites. In addition, no photodecomposition would be expected to occur during the specimen collection process, since light would penetrate very poorly into the tissue samples.

The pattern of tissue distribution of 7-deoxynogarol (Fig. 1) does not correlate well with relative blood-flow rates to different tissues [8]. This observation suggests that human tissue distribution of 7-deoxynogarol conforms more to a membrane-limited model of drug distribution than to a flow-limited model [1].

The very low concentration of 7-deoxynogarol found in tissue after day 27 contrasts to our previous observations with cisplatin [6, 12, 16], mitoxantrone [17], and doxorubicin [23] and suggests that menogaril and its metabolites are less tightly bound to tissues than are the other drugs that we have studied. The lack of retention of the parent compound in tissues is in keeping with the apparent lack of accumulation of menogaril in plasma on its repeated administration to patients; the plasma pharmacokinetics are the same on day 1 as on subsequent days of a 5-day course [4]. One might speculate that this lack of prolonged drug retention in tissues constitutes part of the reason that menogaril appears to have a lower propensity to cause organ damage [9] than do cisplatin, mitoxantrone, and doxorubicin.

It is interesting that 7-deoxynogarol reached relatively high concentrations in the lung. The only tissue containing any parent compound was the lung, which also accounted for two of only seven tissue samples in which *N*-demethylmenogaril could be detected. This observation is in agreement with the results obtained in animal studies, in which the lung achieved high menogaril concentrations [9]. In our clinical studies, some patients have developed cough and chronic dyspnea while taking menogaril, suggesting pulmonary toxicity [19]. One might speculate that prolonged high lung concentrations of 7-deoxynogarol might have been responsible for this. However, the lack of substantial large-bowel or hepatic toxicity of menogaril (despite high 7-deoxynogarol concentrations) indicates that there is probably an element of individual tissue-specific susceptibility to a given dose of menogaril.

Unfortunately, autopsy lung tissue was not available for menogaril assay from the single patient who had received menogaril i.v. Hence, although apparent lung toxicity was seen more often in patients treated i.v. than in those given oral menogaril [19, 21, 25], we cannot comment on the relative pulmonary 7-deoxynogarol concentrations resulting from i.v. versus oral administration of menogaril. In fact, one cannot draw many conclusions from a comparison of the results obtained in this single patient with those obtained in the seven patients who had received oral menogaril, but it should be noted that relatively low concentrations of 7-deoxynogarol were detected in the liver and large bowel of this one patient and that *N*-demethylmenogaril was found relatively frequently in the tissues of this patient (4 of 14 tissues tested). This observation raises the question as to whether the route of menogaril administration might affect its distribution and metabolism.

Menogaril has minimal cardiotoxicity in animals [9], and cardiac toxicity has been very uncommon in the clinical studies done to date. 7-Deoxynogarol achieved relatively low cardiac concentrations, the heart ranking only as the 9th of 18 organs tested, whereas in a study of mitoxantrone it ranked as the 3rd of 21 organs tested [17], and high cardiac concentrations of doxorubicin and doxorubicinol were found in patients who had received doxorubicin antemortem [23]. These comparisons of menogaril with mitoxantrone and doxorubicin lead us to speculate that the relatively low degree of cardiotoxicity of menogaril may be due to low cardiac drug concentrations.

With the majority of drugs we have studied in the past, we have not been able to detect any difference in drug

concentrations between intracerebral tumors and extracerebral tumors [11, 13, 20, 22]. The major exceptions to this have been etoposide [15] and mitoxantrone [17], although the differences in mitoxantrone concentrations were probably due more to differences in the time from the last treatment to death than to the tumor location. Too few tumor samples were available for us to draw firm conclusions with respect to menogaril, but for those tumor samples available, concentrations were lower in intracerebral than in extracerebral tumor deposits. In our phase I studies of menogaril, we noted activity against gliomas [19, 21], but we could not confirm this finding in subsequent phase II studies [26].

As with other drugs we have studied previously [12–14, 17, 20], drug concentrations in tumors were comparable with those in other tissues, with the exception that the concentrations detected in brain tumors (where the blood-brain barrier is usually disrupted) were higher than those found in the surrounding brain tissue. Hence, there was no evidence of preferential augmentation or reduction of the uptake of menogaril or its metabolites into tumors as compared with normal tissues.

A single patient had tumor present in the liver as well as two other organs (adrenal and prostate gland). The hepatic tumor tissue had higher 7-deoxynogarol concentrations than did tumor tissue from the two other sites. Again, firm conclusions cannot be drawn from such limited data, but we have also found hepatic tumors to have higher drug concentrations than tumors in other sites for cisplatin [12, 18] and mitoxantrone [17].

In summary, the major drug species found in human autopsy-tissues after antemortem administration of menogaril was the metabolite 7-deoxynogarol. We postulate that menogaril's occasional pulmonary toxicity may be due to high lung concentrations of 7-deoxynogarol, and we also speculate that its low degree of cardiac toxicity may be due to the attainment of relatively low cardiac muscle concentrations.

Acknowledgements. We thank the staff of the Pathology Department of the Ottawa General Hospital for helping to collect samples, and Dr. Patrick J. McGovern of the Upjohn Pharmaceutical Company for supplying the menogaril and its metabolites used as standards in our assays. Some of the data herein were presented at the annual meeting of the American Association of Cancer Research, May 1991, in Houston, Texas [23].

References

1. Bischoff KB (1975) Some fundamental considerations of the application of pharmacokinetics to cancer chemotherapy. Cancer Chemother Rep 59: 777–793
2. Cummings J, McArdle CS (1986) Studies on the in vivo disposition of Adriamycin in human tumours which exhibit different responses to the drug. Br J Cancer 53: 835–838
3. Dodion P, Egorin MJ, Engisch KL, Bachur NR (1985) Metabolism and disposition of menogaril (NSC 269148) in the rabbit. Cancer Res 45: 5352–5357
4. Egorin MJ, Van Echo DA, Whitacre MY, Forrest A, Sigman LM, Engisch KL, Aisner J (1986) Human pharmacokinetics, excretion, and metabolism of the anthracycline antibiotic menogaril (7-OMEN, NSC 269148) and their correlation with clinical toxicities. Cancer Res 46: 1513–1520
5. Eisenhauer EA, Pritchard KI, Perrault DJ, Verma S, Pater JL (1990) Activity of intravenous menogaril in patients with previously untreated metastatic breast cancer. A National Cancer Institute of Canada Clinical Trials Group study. Invest New Drugs 8: 283–287
6. Gregg RW, Molepo JM, Montpetit VJA, Mikhael NZ, Redmond D, Gadia M, Stewart DJ (1992) Cisplatin neurotoxicity – the relationship between dosage, time, platinum concentration in neurological tissue and morphological evidence of toxicity. J Clin Oncol 10: 795–803
7. Long HJ, Powis G, Schutt AJ, Moertel CG (1987) Phase I and pharmacokinetic study of menogaril administered as a 72-hour continuous iv infusion. Cancer Treat Rep 71: 593–598
8. Mapleson W (1963) An electric analogue for uptake and exchange of inert gases and other agents. J Appl Physiol 18: 197–204
9. McGovern JP, Nelson KD, Lassus M, Cradock JD, Plowman J, Christopher JP (1984) Menogaril: a new anthracycline agent entering clinical trials. Invest New Drugs 2: 359–367
10. Peng YM, Alberts DS, Salmon SW, Davis TP (1984) A method for the simultaneous measurement of the anthracycline derivative 4'-deoxydoxorubicin and its metabolites by reversed phase liquid chromatography. Invest New Drugs 2: 227–280
11. Stewart DJ, Leavens M, Friedman J, Benjamin RS, Moore EC, Bodey GP, Valdivieso M, Burgess MA, Wiseman C, Loo T (1980) Penetration of *N*-(phosphonacetyl)-L-aspartate into human central nervous system and intracerebral tumor. Cancer Res 40: 3163–3166
12. Stewart DJ, Benjamin RS, Luna M, Seifert WE, Loo TL (1982) Human tissue distribution of platinum after *cis*-diammine-dichloroplatinum. Cancer Chemother Pharmacol 10: 51–54
13. Stewart DJ, Lu K, Benjamin RS, Leavens M, Luna M, Yap HY, Loo TL (1983) Concentrations of vinblastine in human intracerebral tumor and other tissues. J Neurooncol 1: 139–144
14. Stewart DJ, Zhengang G, Lu K, Savaraj N, Feun LG, Benjamin RS, Keating MJ, Loo TL (1984) Human tissue distribution of 4'-(9-acridinylamino)-methanesulfon-*m*-aniside (NSC 14159, AMSA). Cancer Chemother Pharmacol 12: 116–119
15. Stewart DJ, Richard M, Hugenholtz H, Dennery J, Belanger R, Gerin-Lajoie J, Montpetit V, Nundy D, Prior J, Hopkins H (1984) Penetration of VP-16 (etoposide) into human intracerebral and extracerebral tumors. J Neurooncol 2: 133–139
16. Stewart DJ, Mikhael NZ, Nanji AA, Kacew S, Howard K, Hirte W, Maroun JA (1985) Renal and hepatic concentrations of platinum: relationship to cisplatin time, dose, and nephrotoxicity. J Clin Oncol 3: 1251–1256
17. Stewart DJ, Green RM, Mikhael NZ, Montpetit V, Thibault M, Maroun JA (1986) Human autopsy-tissue concentrations of mitoxantrone. Cancer Treat Rep 70: 1255–1261
18. Stewart DJ, Mikhael NZ, Nair RC, Kacew S, Montpetit V, Nanji A, Maroun JA, Howard K (1988) Platinum concentrations in human autopsy tumor samples. Am J Clin Oncol 11: 152–158
19. Stewart DJ, Maroun JA, Verma S, Perrault D, Earhart R (1989) Phase I study of weekly intravenous administration of menogaril to adults with solid tumors. Am J Clin Oncol 12: 511–518
20. Stewart DJ, Grewaal D, Green RM, Mikhael N, Montpetit V, Redmond D (1989) Adriamycin concentrations in human autopsy intracerebral and extracerebral tumors. J Neurooncol 7 [Suppl]: S27
21. Stewart DJ, Verma S, Maroun JA, Robillard L, Earhart RH (1990) Phase I study of oral menogaril administered on a once weekly schedule. Invest New Drugs 8: 43–52
22. Stewart DJ, Molepo JM, Green R, Hugenholtz H, Lamothe A, Redmond D, Montpetit V, Mikhael N (1990) Factors affecting tumor cisplatin levels. Proc Am Assoc Cancer Res 31: 180
23. Stewart D, Grewaal D, Green R, Redmond D (1991) Anthracycline levels in human autopsy heart tissue (abstract). Proc Am Assoc Cancer Res 32: 205
24. Stewart D, Eisenhauer E, Skillings J, Pritchard K, Buckman R, Vandenberg T, Verma S, Aitken S, Norris B (1992) Phase II study of

oral menogaril as first line treatment for advanced breast cancer: a National Cancer Institute of Canada Clinical Trials Group study. Ann Oncol 3: 201–204

25. Stewart DJ, Aitken SE, Verma S, Maroun JA, Robillard L, Touchie M, Prosser IA, Earhart RH (1992) Phase I study of oral menogaril administered daily for 14 consecutive days. Ann Oncol 3: 401–403
26. Stewart DJ, Hugenholtz H, DaSilva V, Benoit B, Richard M, Verma S, Earhart R, Robillard L (1992) Phase II study of weekly intravenous menogaril in the treatment of recurrent astrocytomas in adults. J Neurooncol 13: 183–188
27. Zanette ML, Tirelli U, Sorio R, Zadro D, Figoli F, Monfardini S, D'Incalci M (1987) Pharmacokinetics of 7-con-*O*-methylnogarol in patients with solid tumors. Cancer Chemother Pharmacol 20: 67–70