Cancer Chemother Pharmacol (1994) 34: 153–158

Cancer Chemotherapy and Pharmacology

Effect of DNA-repair-enzyme modulators on cytotoxicity of L-phenylalanine mustard and *cis*-diamminedichloroplatinum (II) in mammary carcinoma cells resistant to alkylating drugs

Moulay Alaoui-Jamali[1], Bel-Baraka Loubaba[1], Schecter Robyn[1], Haim Tapiero[2], Gerald Batist[1]

[1] Lady Davis Institute for Medical Research and McGill University, Montreal, Canada
[2] Paul Brousse Hospital-CNRS, Villejuif, France

Received: 24 May 1993/Accepted: 7 January 1994

Abstract. We investigated the effect of DNA-repair-enzyme inhibitors on L-phenylalanine mustard (L-PAM) and *cis*-diamminedichloroplatinum (II) (CDDP) cytotoxicity in rat mammary-carcinoma MatB cells sensitive (WT) and resistant (MLNr) to bifunctional alkylating drugs. Among the modulators tested, the combination of arabinofuranosylcytosine (Ara-C) and hydroxyurea (HU) significantly increased the sensitivity of the cells to CDDP and, to a lesser extent, L-PAM as compared with cells treated with drug alone. The modulation effect of HU+Ara-C on CDDP and L-PAM cytotoxicity was more effective when intracellular glutathione (GSH) was depleted by L-buthionine-(S,R)-sulfoximine (BSO). This was also associated with a significant increase in DNA-DNA interstrand cross-links. Caffeine also sensitized both WT and MLNr cells to the cytotoxic effect of L-PAM and CDDP, and this effect was potentiated in GSH-depleted cells. No significant effect was observed with other repair modulators such as aphidicolin, 3-aminobenzamide, novobiocin, or etoposide. These results show (a) that inhibition of DNA repair by HU+Ara-C or caffeine could be a target for modulation of bifunctional alkylating-drug resistance and (b) that GSH depletion renders resistant cells more susceptible to the repair-enzyme modulators, suggesting that intracellular GSH may be involved in the regulation of some of these enzymes. Our results also indicate that a combination of a number of modulators may offer an advantage over the use of a single modulator in tumor resistance that may be associated with multifactorial mechanisms.

This work was supported in part by the Quebec Lung Association and the National Cancer Institute of Canada

Abbreviations: 3-Aminobenzamide, 3-AB; adenosine diphosphate, ADP; aphidicolin, APD; arabinofuranosylcytosine, Ara-C; 1-β-D-L-buthionine-(S,R)-sulfoximine, BSO; *cis*-diamminedichloroplatinum (II) (cisplatin), CDDP; glutathione, GSH; glutathione-S-transferase, GST; hydroxyurea, HU; L-phenylalanine mustard (melphalan), L-PAM

Correspondence to: Moulay Alaoui-Jamali, Lady Davis Institute for Medical Research, Room 523, 3755 Cote-Ste Catherine Road, Montreal, Canada H3T 1E2

Introduction

Alkylating agents constitute a major class of anticancer drugs with well-established activity against human cancers, including carcinoma of the breast [3]. Their effectiveness in curing cancer, however, is limited by a number of factors, including the development of tumor resistance. The latter is a common cause of relapse in cancer patients following an initial response to chemotherapy.

The development of resistance to a single alkylating agent is often associated with cross-resistance to other alkylating drugs and, under some conditions, to natural products as well as radiation [13]. Major mechanisms involved in resistance to alkylating drugs include (a) decreased cellular drug accumulation through alterations in specific transport carriers or overexpression of specific membrane glycoprotein(s) [8], (b) altered drug metabolism, (c) enhanced drug detoxification due to the conjugation of glutathione (GSH) to drug or to drug-DNA adducts through glutathione-S-transferase (GST) catalysis [26], and (d) enhanced repair of drug-DNA monoadducts or DNA cross-links [21]. Although these mechanisms taken individually have proved to be of fundamental interest and have shown encouraging results in experimental models, their clinical importance remains controversial. Drug resistance is often associated with several distinct mechanisms within the same tumor. Because of this multifactorial process, it is unlikely that a single modulation agent will be clinically relevant on its own. Clinical experience with anticancer drugs has shown that combination regimens are more successful than single agents used alone. Based on this concept, incorporation of two or more modulators with different targets in the standard regimens may be more efficient in overcoming drug resistance.

We have previously reported that drug-induced DNA-DNA cross-links are diminished in rat mammary-carcinoma MatB cells originally selected for resistance to L-phenylalanine mustard (L-PAM) [1]. Considering that the cytotoxic effect of alkylating drugs is in part dependent upon the balance between DNA lesions and DNA repair, we investigated the effect of some enzyme inhibitors,

Table 1. Cross-resistance profile of MLNr cells

Drug	IC_{50}, μM		Relative factor of resistance[a]
	WT	MLNr	
L-PAM	0.26 ± 0.02	27.75 ± 2.3	107
Mechlorethamine	0.04 ± 0.01	3.45 ± 0.3	96
Chlorambucil	0.63 ± 0.03	38.50 ± 2.6	61
BCNU	2.90 ± 0.40	138.00 ± 9.3	48
CDDP	0.22 ± 0.02	17.50 ± 1.9	80
Mitomycin C	0.14 ± 0.02	1.25 ± 0.2	9
Mitoxantrone	9.10 ± 0.60	21.10 ± 1.9	2.3

The IC_{50} value was determined graphically from the survival curve as the concentration inhibiting 50% of cell growth (average of at least 5 experiments ± SE). BCNU, Carmustine

[a] Ratio of IC_{50}-MLNr/IC_{50}-WT

known to interfere with DNA repair processes, on cell survival and DNA-cross-linking in parental cells (MatB-WT) and L-PAM-resistant cells (MatB-MLNr). These inhibitors included arabinofuranosylcytosine (Ara-C) and caffeine (inhibitors of replicative and repair synthesis), aphidicolin (APD; polymerase α and γ inhibitor), 3-aminobenzamide [3-AB; poly(ADP-ribose)polymerase inhibitor], and novobiocin and etoposide (VP16) (topoisomerase II inhibitors). Since MLNr cells exhibit a 2-fold increase in GSH content [17] and because of evidence that GSH may interact with some repair processes [9, 15], we compared the effect of repair modulators on GSH-depleted cells.

Materials and methods

Drugs. L-PAM, APD, Ara-C, caffeine, L-buthionine-(S,R)-sulfoximine (BSO), and novobiocin were obtained from Sigma Chemical Company. *cis*-Diamminedichloroplatinum (II) (CDDP) was obtained from David Bull Laboratories Pty. Ltd. (Canadian distributor, Horner). 3-AB was a gift from Dr. Guy Poirier (Laval University, Quebec). VP16 was obtained from Bristol Laboratories (Syracuse, N.Y.). [^{14}C]-Thymidine (spec. act., 51.7 mCi/mmol) and [^{3}H]-thymidine (spec. act., 20 Ci/mmol) were obtained from New England Nuclear.

Cell culture and cytotoxicity assay. The parental drug-sensitive cell line MatB-13162 (WT) was originally obtained from a rat mammary adenocarcinoma. An L-PAM-resistant cell line (MLNr) was selected by continuous exposure of WT cells to L-PAM as described elsewhere [17]. Cells were maintained in culture in alpha-minimal essential medium (α-MEM, Gibco) supplemented with 1.3% sodium pyruvate, 2.6% glutamine, 1.3% nonessential amino acids, 10% fetal bovine serum, and 100 units gentamycin/ml in a humidified atmosphere containing 5% CO_2. For modulation assays, exponentially growing cells were first treated with the modulator for 18 h and were then subjected to continuous exposure to alkylating agents. This procedure was based on preliminary experiments in which pretreatment with modulators was found to be more effective than simultaneous treatment (data not shown). BSO was used at nontoxic concentrations of 50 (50% GSH depletion) and 100 μM (70% GSH depletion) [1]. Drug cytotoxicity was determined 72 h later using a 3-(4,5-dimethylthiazo-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay as described previously [1].

DNA damage studies. DNA-DNA interstrand cross-links were quantified by alkaline elution based on the protocol described by Kohn et al. [10]. The alkaline elution conditions have been described elsewhere [1].

Statistical analysis. Student's two-tailed *t*-test was used to compare the cytotoxicity of drugs in the absence and presence of each modulator.

Results

In addition to drugs described previously [1, 17], MLNr cells were found to be cross-resistant to mitomycin C and mitoxantrone (Table 1), whereas there was no cross-resistance to Ara-C, methotrexate, HU, fluorouracil, VP16, or caffeine (data not shown). The differences in the factors of resistance published previously [1, 17] and those reported in this study are related to the assay and conditions used to assess the cytotoxicity (MLNr cells are 16- and 107-fold resistant to L-PAM as determined by clonogenic assay in agar and by MTT assay, respectively). We investigated the modulation effect on L-PAM and CDDP because these agents constitute the prototype of two major classes of anticancer drugs and they have different mechanisms of cytotoxicity: DNA intrastrand cross-links and, to a lesser extent, interstrand cross-links have been correlated with CDDP cytotoxicity [6, 29], whereas DNA interstrand cross-links have been found to be most relevant to L-PAM cytotoxicity [29].

Preliminary experiments were established to determine a nontoxic concentration of each modulator. Using the MTT assay, the maximal nontoxic concentrations for both WT and MLNr cells were found to be: HU, 0.5 mM; Ara-C, 5 nM; caffeine, 0.5 mM; 3-AB, 0.5 mM; novobiocin, 100 μM; and VP16, 0.01 μM. The nontoxic concentration of APD was 0.005 and 0.01 μg/ml for WT and MLNr cells, respectively. These concentrations were used for modulation studies. For GSH depletion, we used nontoxic concentrations of 50 and 100 μM BSO [1].

As reported in Table 2, the modulators tested had only a slight effect on L-PAM cytotoxicity in both WT and MLNr cells in the absence of GSH depletion. The combination of Ara-C and HU sensitized WT and MLNr cells to L-PAM by 23% and 17%, respectively, as compared with cells treated with L-PAM alone, whereas Ara-C and HU alone had no effect. An approximately 22% increase in L-PAM cytotoxicity was also observed in both cell lines following pretreatment with caffeine. For CDDP, the most effective modulation was obtained with the combination of Ara-C and HU (Table 3). As compared with cells treated with CDDP alone, there were increases of 24% and 37% in CDDP toxicity in WT and MLNr cells, respectively ($P < 0.05$).

As shown in Tables 2 and 3, depletion of GSH by 50 μM BSO (50% depletion as compared with untreated cells) increased L-PAM cytotoxicity by approximately 25% and 16%, respectively, and CDDP cytotoxicity by 12% and 17%, respectively, in MLNr and WT cells as compared with non-GSH-depleted cells. In GSH-depleted cells, the combination of HU and Ara-C was more effective in enhancing L-PAM and CDDP cytotoxicity. As compared with cells treated with drug alone, increases of 40% and 47% in CDDP cytotoxicity and of 39% and 46% in L-PAM cytotoxicity were observed in WT and MLNr cells pretreated with BSO in the presence of HU+Ara-C, respectively ($P < 0.05$). Additional GSH depletion (when cells were

Table 2. Effect of DNA-repair modulators on the cytotoxic effect of L-PAM

	-BSO	DMF	+50 μ*M* BSO	DMF	+100 μ*M* BSO	DMF
WT cells:						
Control	0.31±0.052	1	0.26±0.028	1	0.25±0.06	1
HU	0.29±0.041	1.1	0.21±0.015	1.2	0.20±0.05	1.3
Ara-C	0.30±0.031	1	0.24±0.031	1.1	0.22±0.10	1.2
HU+Ara-C	0.24±0.051	1.3	0.16±0.028**	1.6	0.18±0.01*	1.4
Caffeine	0.23±0.031	1.4	0.18±0.013	1.4	0.21±0.05	1.2
MLNr cells:						
Control	30.33±4.35	1	22.70±2.15	1	12.34±0.16	1
HU	26.33±3.15	1.2	21.50±1.12	1.1	10.15±1.12	1.2
Ara-C	30.00±2.33	1	24.00±1.93	1	11.33±0.65	1.1
HU+Ara-C	25.30±2.25	1.2	12.30±3.20**	1.9	6.12±0.50**	2.0
Caffeine	23.90±2.13	1.3	17.70±2.39*	1.3	8.35±1.15*	1.5

DMF, Dose-modifying factor
*P <0.05; **P <0.01

Table 3. Effect of DNA-repair modulators on the cytotoxic effect of CDDP

	-BSO	DMF	+50 μ*M* BSO	DMF	+100 μ*M* BSO	DMF
WT cells:						
Control	0.17±0.026	1	0.15±0.05	1	0.16±0.02	1
HU	0.13±0.016	1.3	0.13±0.037	1.2	0.15±0.03	1.1
Ara-C	0.22±0.028	1	0.18±0.049	0.8	0.17±0.05	0.9
HU+Ara-C	0.13±0.05	1.3	0.09±0.027*	1.7	0.11±0.01*	1.5
Caffeine	0.15±0.027	1.1	0.09±0.037*	1.7	0.11±0.01*	1.5
MLNr cells:						
Control	16.17±1.53	1	13.50±0.45	1	11.34±1.10	1
HU	12.23±1.12	1.3	9.70±1.54*	1.4	7.25±0.77*	1.6
Ara-C	16.90±1.78	1	14.11±0.65	1	9.66±0.55	1.2
HU+Ara-C	10.20±1.30*	1.6	7.10±1.51**	1.9	5.23±1.35**	2.2
Caffeine	13.50±1.40	1.2	11.30±2.21	1.2	8.93±1.12	1.3

DMF, Dose-modifying factor
*P <0.05; **P <0.01

treated with 100 μ*M* BSO, which gave about 70% GSH depletion as compared with untreated cells) further increased the cytotoxic effect of L-PAM and CDDP in resistant cells (Tables 2, 3). Caffeine also sensitized both WT and MLNr cells to the cytotoxic effect of L-PAM and CDDP (approximately 20% increases as compared with drug alone; P <0.05) and this effect was increased in GSH-depleted cells (Tables 2, 3). With both HU+Ara-C and caffeine, Student's t-test revealed a significant difference in the modulation effect between non-GSH-depleted and GSH-depleted cells (P <0.05). APD had a slight but nonsignificant effect on CDDP sensitization, whereas novobiocin, VP16, and 3-AB had no effect at all when used at the maximal nontoxic concentration (data not shown).

Figures 1 A and 1 B show that with both L-PAM and CDDP, there was a decrease in DNA-DNA cross-link formation in MLNr cells as compared with WT cells. The low level of cross-linking obtained with L-PAM in MLNr cells has previously been reported [1]. As compared with WT cells, MLNr cells demonstrated decreases of 43% and 61% in CDDP-induced DNA-DNA cross-links in MLNr cells at 6 and 20 h following incubation in drug-free medium, respectively (Fig. 1 B). We compared the cross-link-inducing ability of L-PAM and CDDP in the presence of HU and Ara-C only, because this combination proved to be more potent than the other modulators tested (Tables 2, 3). The combination of HU+Ara-C had no significant effect on L-PAM-induced cross-linking, but 25% and 40% increases in DNA-DNA cross-link formation was observed with CDDP at 6 and 20 h following incubation in drug-free medium, respectively. The effect of GSH depletion on DNA cross-links was investigated using 50 μ*M* BSO only. A concentration of 100 μ*M* BSO was found to inhibit cell growth under the conditions used. The combination of HU and Ara-C had a greater effect on DNA cross-linking in GSH-depleted cells than in non-GSH-depleted cells. There were increases of 35% and 52% in CDDP-induced cross-linking after 6 and 20 h of incubation, respectively. With L-PAM (Fig. 1 A), increases of 30% and 23% in DNA-DNA cross-links was observed at 6 and 20 h, respectively, versus only a slight but not significant effect seen in non-GSH-depleted cells. With all the combinations, a significant difference in the cross-link-inducing ability of L-PAM was evident between WT and MLNr cells (P <0.05).

Discussion

This study was designed to elucidate the mechanisms of decreased DNA-DNA cross-linking induced by alkylating

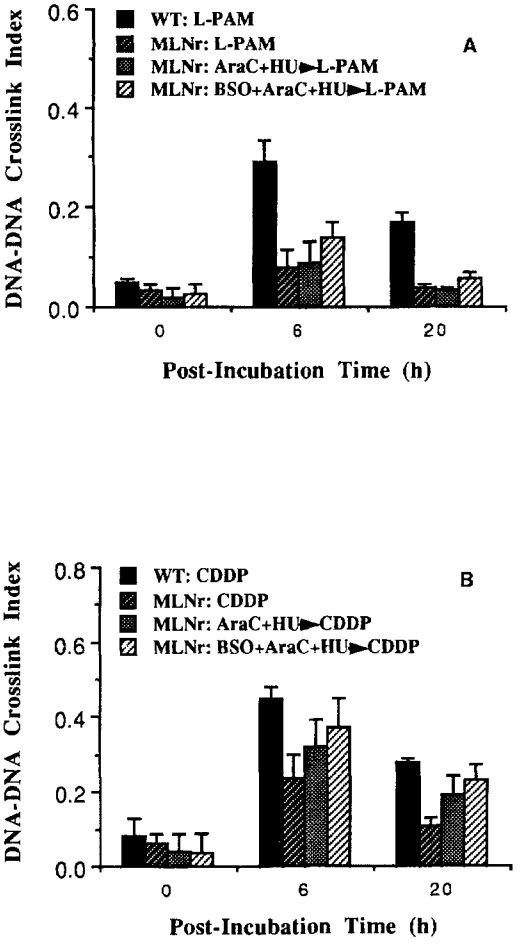

Fig. 1A, B. DNA-DNA cross-links induced by **A** L-PAM and **B** CDDP. Exponentially growing cells were treated with the combination of 5 n*M* Ara-C and 0.5 m*M* HU in the presence or absence of 50 μ*M* BSO. After 18 h incubation, medium was removed and cells were treated with 30 μ*M* L-PAM (**A**) or 30 μ*M* CDDP (**B**) in the presence or absence of Ara-C+HU. After 1 h treatment, drug was removed and cells were incubated in drug-free medium containing Ara-C+HU at the same concentrations. At the indicated time, cells were prepared for alkaline elution. Data represent mean values ± SD for 2 independent experiments. $^*P < 0.05$ as compared with MLNr cells treated with L-PAM or CDDP alone

drugs in drug-resistant mammary carcinoma cells and to establish effective modulation strategies. MLNr cells are a typical tumor model in which a multitude of mechanisms are associated with resistance, including alterations in drug transport, increases in GSH levels and GST activity, and a very low level of drug-induced DNA cross-link formation [1, 17]. In addition, there is enough evidence to suggest that altered drug-DNA interaction or increased DNA repair may be involved, at least in part, in the acquisition of drug resistance in this model:

1. Depletion by BSO of intracellular GSH to a level comparable with that seen in WT cells has only a partial effect on the sensitization of MLNr cells.
2. Ethacrynic acid, an inhibitor of GST, used alone or in combination with BSO has only a partial effect, whereas in other cell lines in which resistance is specifically associated with alterations in GSH and GST, these modulators can sensitize resistant cells to drug to the same level as the WT cells [28].
3. L-PAM has been found to be distributed in the nuclei of resistant cells and its cellular metabolism has been found to be identical between WT and MLNr cells [1].
4. CDDP accumulation as determined by atomic spectrophotometry was identical between the two cell lines (the accumulation level of 30 μ*M* CDDP after 3 h incubation was 348.5 ± 60.8 and 320.5 ± 85.1 pmol/10^6 cells in WT and MLNr cells, respectively; however, the removal of CDDP-induced DNA cross-links was significantly lower in MLNr cells).

By using repair inhibitors it may be possible to localize a specific pathway involved in the repair of DNA damage induced by alkylating drugs and to establish modulation strategies for resistant cells.

In MLNr cells, none of the modulators tested was found to be very effective in modulating L-PAM cytotoxicity except for caffeine and, to a smaller extent, HU+Ara-C. No significant difference was detected in either case. However, the combination of HU-Ara-C was found to be more efficient in L-PAM modulation in GSH-depleted cells. In contrast, HU+Ara-C was more effective in modulating the cytotoxicity of CDDP in non-GSH-depleted cells, and this effect was further increased in GSH-depleted cells. The combination of HU+Ara-C also increased CDDP- and L-PAM-induced DNA-DNA cross-link formation, and this effect was significantly increased in GSH-depleted cells. Considering that (a) HU and Ara-C are inhibitors of both replicative and repair synthesis [5, 11, 14, 16, 25] and (b) GSH quenches drug-DNA monoadducts, thereby reducing DNA cross-link formation [2], and also interferes with repair enzymes such as DNA ligases [12, 13, 15], our results suggest that resistance to alkylating drugs could be manipulated by altering DNA repair processes. GSH depletion by BSO sensitizes cells to the effect of HU+Ara-C, suggesting that GSH may interfere with some repair enzymes. The potent efficiency of HU+Ara-C in modulating CDDP cytotoxicity suggests that the repair mechanism(s) of this drug may be distinct from that of L-PAM. Our results support previous reports on the effect of HU+Ara-C on the cytotoxicity of CDDP analogues [22, 23] and carmustine (BCNU) [24]. The sensitization effect obtained with caffeine may be related to an interaction with the repair of damage induced by L-PAM and CDDP since it is known that this xanthine interferes with excision repair mechanisms. Using *Escherichia coli*, Selby and Sankar [18] have reported that caffeine inhibits DNA repair by at least two mechanisms: (1) interference with specific DNA-binding proteins and (2) a nonspecific mechanism involving inhibition of the nucleotide excision repair of (A)BC excinuclease. However, the importance of these mechanisms in mammalian cells remains to be determined.

The repair mechanisms of alkylating drugs are yet unknown. The multifactorial mechanism of resistance and the lack of information on the nuclear distribution of enzyme inhibitors and their effectiveness against residual repair enzymes makes it difficult to explain the partial effect obtained with these modulators, since the level of cross-linking observed in MLNr cells was significantly different

from that seen in WT cells. That the other modulators such as VP16 and novobiocin (topoisomerase II inhibitors [4]), 3-AB {Poly(ADP-ribose)polymerase inhibitors [19]}, and APD (polymerase α and β inhibitor [20]) had no effect suggests that the enzymes they affect are not determinant in the repair of L-PAM- or CDDP-induced DNA damage in MatB cells. However, we cannot completely rule out the importance of these enzymes in alkylating drug resistance. For example, DNA polymerases α and β are involved in DNA repair and may operate on the same lesions or independently on different lesions [27]. It has been reported that polymerase α is involved in the repair of large gaps and polymerases α and β are involved in the repair of middle-sized gaps, whereas polymerase β is more important in the repair of small (i.e., X-ray-induced) gaps. Previous investigations have shown that the repair of damage induced by UV irradiation involves only polymerase α, whereas the repair of damage caused by other chemicals such as mitomycin C, dimethylsulfate, neocarzinostatin, and benzo(a)pyrene involves polymerases α and β [7, 27]. It is likely that various polymerase enzymes may be involved, and combinations of their inhibitors may be more efficient than APD alone. It is also possible that the repair of L-PAM- or CDDP-DNA adducts requires a small amount of DNA precursors or repair enzymes such that the residual precursor pool (i.e., endogenous levels of nucleotides or enzymes) following treatment with modulators may be sufficient for efficient repair. More effective modulators of DNA-repair enzymes may be more efficient.

In conclusion, our data show that DNA-repair-enzyme inhibitors are less effective in modulating L-PAM cytotoxicity as compared with CDDP cytotoxicity in non-GSH-depleted cells, which may suggest that different repair mechanisms are involved with these two drugs. The combination of HU and Ara-C or caffeine is more efficient in modulating L-PAM and CDDP cytotoxicity in GSH-depleted cells. Our data suggest that modulation strategies based on the use of multiple inhibitors may offer an advantage over the application of a single agent.

References

1. Alaoui-Jamali MA, Panasci L, Centurioni MG, Schecter R, Lehnert S, Batist G (1992) Nitrogen mustard-DNA interaction in melphalan-resistant mammary carcinoma cells with elevated intracellular glutathione and glutathione-S-transferase activity. Cancer Chemother Pharmacol 30: 341–347
2. Ali-Osman F (1989) Quenching of DNA crosslink precursors of chloroethylnitrosoureas and attenuation of DNA interstrand crosslinking by glutathione. Cancer Res 49: 5258–5261
3. Carter KS (1983) The interaction of irradiation as part of primary breast cancer therapy with the use of adjuvant chemotherapy. In: Harris JR, Hellman S, Silen W (eds) Conservative management of breast cancer. New surgical and radiotherapeutic techniques. J. B. Lippincott, Philadelphia, pp 289–298
4. D'Arpa P, Liu LF (1989) Topoisomerase-targeting antitumor drugs. Biochim Biophys Acta 989: 163–177
5. Dunn WC, Regan JD (1979) Inhibition of DNA excision repair in human cells by arabinofuranosylcytosine: effect on normal and xeroderma pigmentosum cells. Mol Pharmacol 15: 367–374
6. Fichtinger-Schepman AMJ, Lohman PHM, Berends F, Reedyk J, Van Oosteron AT (1988) Interactions of the anti-tumor drug cisplatin with DNA in vitro and in vivo. IARC Sci Publ 78: 83–99
7. Ishiguro T, Otsuda F, Ochi T, Ohsawa M (1987) Involvement of DNA polymerases in the repair of DNA damage by benzo(a)pyrene in cultured Chinese hamster cells. Mutat Res 184: 57–64
8. Kawai K, Kamatani N, Georges E, Ling V (1990) Identification of a membrane glycoprotein overexpressed in murine lymphoma sublines resistant to *cis*-diamminedichloroplatinum(II). J Biol Chem 265: 13137–13142
9. Ketterer B, Meyer DJ (1989) Glutathione transferases: a possible role in the detoxification and repair of DNA and lipid hydroperoxides. Mutat Res 214: 33–40
10. Kohn KW, Ewig RAG, Erickson LC, Zwelling LA (1981) Measurement of strand breaks and crosslinks by alkaline elution. In: Freidberg EC, Hanawalt PC (eds) DNA repair: a laboratory manual of research procedures, vol 1, part B. Marcel Dekker, New York, pp 379–401
11. Kuchta DR, Ilsley D, Kravig DK, Schubert S, Harris B (1992) Inhibition of DNA primase and polymerase α by arabinofuranosylnucleoside triphosphates and related compounds. Biochemistry 31: 4720–4728
12. Lai Gi-M, Ozols FR, Young RC, Hamilton TC (1989) Effect of glutathione on DNA repair in cisplatin-resistant human ovarian cancer cell lines. J Natl Cancer Inst 81: 535–539
13. Lehnert S, Greene D, Batist G (1989) Radiation response of drug resistant variants of a human breast cancer cell line. Radiat Res 118: 568–580
14. Mirzayans R, Paterson MC (1991) Differential repair of 1-β-D-arabinofuranosylcytosine-detectable sites in DNA of human fibroblasts exposed to ultraviolet light and 4-nitroquinone-1-oxide. Mutat Res 255: 57–65
15. Rairkar A, Ali-Osman F (1992) Modulation of DNA ligase activities in a BCNU and cisplatin resistant human malignant astrocytoma cell line by glutathione. Proc Am Assoc Cancer Res 33: 41
16. Rbichaud NJ, Fram RJ (1987) Potentiation of araC induced cytotoxicity by hydroxyurea in LoVo colon carcinoma cells. Biochem Pharmacol 36: 1673–1677
17. Schecter LR, Woo A, Duong M, Batist G (1991) In vivo and in vitro mechanisms of drug resistance in a rat mammary carcinoma model. Cancer Res 51: 1434–1442
18. Selby CP, Sankar A (1990) Molecular mechanisms of DNA repair inhibition by caffeine. Proc Natl Acad Sci USA 87: 3522–3525
19. Shall S (1983) ADP-ribosylation, DNA repair, cell differentiation and cancer. In: Miwa M, et al (eds) ADP-ribosylation, DNA repair and cancer. Japan Science Society Press, Tokyo/VNU Science Press, Utrecht, pp 3–25
20. Sheaff R, Ilsley D, Kuchta R (1991) Mechanism of DNA polymerase α inhibition by aphidicolin. Biochemistry 30: 8590–8597
21. Sheibani N, Jennerwein MM, Eastman A (1989) DNA repair in cells sensitive and resistant to *cis*-dichlorodiammineplatinum(II): host cell reactivation of damaged plasmid DNA. Biochemistry 28: 3120–3124
22. Swinnen LJ, Barnes DM, Fisher SG, Albain KS, Fisher RI, Erickson LC (1989) 1-β-D-Arabinofuranosylcytosine and hydroxyurea: production of cytotoxic synergy with *cis*-diamminedichloroplatinum(II) and modifications in platinum-induced DNA interstrand crosslinking. Cancer Res 49: 1383–1389
23. Swinnen LJ, Ellis NK, Erickson LC (1991) Inhibition of *cis*-diammine-1,1-cyclobutane-dicarboxylatoplatinum(II)-induced DNA interstrand cross-link removal and potentiation of *cis*-diammine-1,1-cyclobutanedicarboxylatoplatinum(II) cytotoxicity by hydroxyurea and 1-β-D-arabinofuranosylcytosine. Cancer Res 51: 1984–1989
24. Swinnen LJ, Ellis NK, Marathi U, Erickson LC (1991) Hydroxyurea and AraC inhibit the repair of BCNU-induced DNA interstrand crosslinks. Proc Am Assoc Cancer Res 32: 2504
25. Von Hoff DD, Waddelow T, Forseth B, Davidson K, Scott J, Wahl G (1991) Hydroxyurea accelerates loss of extrachromosomally amplified genes from tumor cells. Cancer Res 51: 6273–6279

26. Waxman JD (1990) Glutathione-S-transferases: role of alkylating agents resistance and possible target for modulation chemotherapy. Cancer Res 50: 6449–6454
27. Yamada K, Hanaoka F, Yamada M (1985) Effects of aphidicolin and/or 2′,3′-dideoxythymidine on DNA repair induced in HeLa cells by four types of DNA-damaging agents. J Biol Chem 260: 10412–10417
28. Yang ZW, Begleiter A, Johnston BJ, Israels GL, Mowat RAM (1992) Role of glutathione and glutathione-S-transferase in chlorambucil resistance. Mol Pharmacol 41: 625–630
29. Zwelling LA, Michaels S, Schwartz H, Dobson PP, Kohn KW (1981) DNA crosslinking as an indicator of sensitivity and resistance of mouse L1210 leukemia to *cis*-diamminedichloroplatinum(II) and L-phenylalanine mustard. Cancer Res 41: 640–649