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Enhancement of cisplatin (DDP) antitumor activity by 3-aminobenzamide in rat ovarian tumors sensitive and resistant to DDP in vivo

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Summary. A cisplatin (DDP)-resistant rat ovarian tumor cell line (O-342/DDP) and its parental sensitive counterpart (O-342) were used to investigate the combination effect of DDP plus 3-aminobenzamide (3-AB), an inhibitor of adenosine diphosphate ribose transferase (ADPRT). Treatment with six doses of DDP in NMRI nude mice bearing O-342/DDP produced an increase in mean survival of only 1 day over that of controls ($P > 0.05$). The addition of nontoxic doses of 3-AB (5 m*M*/kg $\times 6$) increased the mean survival to 6.4 days compared with that obtained with DDP treatment alone ($P < 0.001$). In the sensitive ovarian tumor line (O-342), the combination effect of DDP plus 3-AB was even more impressive: simultaneous treatment of NMRI nude mice bearing O-342 with three doses of DDP plus 3-AB increased the mean survival by 2 weeks and the median survival by 3 weeks over that achieved with DDP treatment alone. Possible mechanisms involved in the potentiation of DDP activity and the possible clinical potential of this combination are discussed.

Introduction

DDP is one of the most successful chemotherapeutic agents in clinical oncology; it is applied with curative intent, especially in the treatment of testicular and ovarian cancer, and is an essential part of the treatment of other cancer types such as head and neck cancer and cancer of the bladder, cervix and lung. For the treatment of ovarian cancer, it has proved to be the most active single agent, with an overall response rate of 86% in combination with surgery [32, 42]. However, its benefit is often hampered by the emergence of resistance. To overcome resistance, several efforts have been made, including high-dose chemotherapy as well as regional and targeted chemotherapy [30]. Using a better understanding of possible resistance mechanisms, several approaches have been followed to reverse resistance, such as enhancement of cellular DDP accumulation by verapamil [26] or hyperthermia [46] and depletion of intracellular GSH by the thiol-modulating agent BSO [21] to prevent binding and inactivation of free DDP. The majority of these attempts, however, have met with limited success, if any [17]; for example, although in some resistant cell lines sensitivity to DDP was partially restored after GSH depletion [2, 15, 22], in other cell lines resistance was not reversible following treatment with BSO [1, 24, 38]. These overall disappointing results were attributed to a multifactorial development of DDP resistance [25].

3-AB is an inhibitor of adenosine-diphosphate-ribose transferase (ADPRT), a chromatin-associated enzyme that catalyzes the transfer of the ADP-ribose moiety from nicotinamide-adenine dinucleotide (NAD) to nuclear protein acceptors as well as the further addition of ADP-ribose moieties to produce a homopolymer [poly(ADP-R)] of up to 70 residues [23, 37]. Although the exact biological function of poly(ADP-R) is not known, it has been reported to be involved in cellular differentiation [20, 34], DNA repair and replication [11, 18] as well as in chromatin structure [5]. The synthesis of ADPRT is stimulated by DNA strand breakage, which can be induced by X-rays, UV irradiation, bleomycin, or alkylating agents [6, 7, 27–29, 33]. These observations suggest that through an inhibition of DNA repair, the antitumor effect of DNA-targeted cytostatic agents can be enhanced by ADPRT inhibitors. This has been confirmed by several investigators [8, 10, 12–14, 29, 47].

Berger et al. [8] and Yamamoto and Okamoto [47] have observed a significant enhancement of antitumor ac-

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Abbreviations: 3-AB, 3-aminobenzamide; ADP, adenosine diphosphate; ADPRT, adenosine diphosphate ribose transferase; BCNU, 1,3-bis-(2-chloroethyl)-1-nitrosourea; BSO, D,L-buthionine-sulfoximine; DDP or cisplatin, *cis*-diamminedichloroplatinum(II); GSH, reduced glutathione; MS, median survival; NA, nicotinamide; NAD, nicotinamide-adenine dinucleotide

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Table 1. Reversal of cisplatin resistance of an animal ovarian tumor (O-342/DDP) by 3-AB in NMRI nude mice

Treatment[a]:			Schedule	Animals	Mean survival	ILS[b] (%)	*P*
0.9% saline	5 mM/kg 3-AB	1 mg/kg DDP		(*n*)	(days, Mean ± SD)		
+	–	–	EOD, days 1–11	10	23.8 ± 3.7	–	–
+	+	–	EOD, days 1–11	9	23.0 ± 3.1	-3.4	>0.05*
+	–	+	EOD, days 1–11	9	24.8 ± 3.1	4.2	>0.05*
–	+	+	EOD, days 1–11	12	31.2 ± 2.3	31.1	<0.001* <0.001**

[a] Drugs were simultaneously given i.p.
[b] ILS (increase in life span vs. untreated controls) = [(treatment – control)/control] × 100
* vs control; ** vs DDP alone (Student's *t*-test)
EOD, every other day

tivity of BCNU and streptozotocin by ADPRT inhibitors. Chen and Pan [10, 12, 13] and Kawamitsu et al. [29] have reported that the ADPRT inhibitors 3-AB and nicotinamide (NA) could potentiate the therapeutic effect of bleomycin in different murine tumor cell lines in vivo. Recently it was reported that the antitumor activity of DDP and 6-thioguanine could significantly be increased by 3-AB [14, 35]. Our previous results indicate that DDP resistance in an animal ovarian tumor cell line (O-342/DDP) is probably associated with an increase in DNA repair [16]. To overcome resistance in this tumor, we carried out combination chemotherapy experiments investigating the activity of DDP plus 3-AB in vivo. In addition, the combination effect of DDP plus 3-AB on the sensitive parental counterpart (O-342) was assessed in vivo.

Materials and methods

Animals and drugs. Female BD IX rats (6–8 weeks of age) and female NMRI nude athymic mice (weighing 20–25 g) were supplied by the Zentralinstitut für Versuchstierzucht (Hannover, FRG) and maintained under standard conditions (25° C room temperature, 66% humidity, 12 h light and 12 h darkness, Macrolon cages, autoclaved standard diet, water ad libitum). NMRI nude athymic mice were supplied with acidified water. 3-AB powder was purchased from Sigma Company (St. Louis, Mo, USA) and dissolved in 0.9% saline immediately before use. DDP stock solution (0.5 mg/ml) was obtained from Behring Werke AG (Marburg, FRG).

Tumor model. The ovarian tumor (O-342) was induced in a female BD IX rat by i.p. injection of ethylnitrosourea (100 mg/kg × 1); the manifestation time was 422 days. Histology of the primary tumor corresponded to a granulosa cell tumor; following i.p. inoculation, tumor growth is highly malignant. Resistance of O-342 to DDP (O-342/DDP) was induced in vivo by the following procedure: BD IX rats bearing O-342 were treated in successive i.p. passages with i.p. doses of 1.2–1.5 mg/kg DDP (2–3 doses in every passage). This treatment was done for about 18 months (ca. 25 passages). Thereafter, i.p. treatment of BD IX rats bearing O-342 with DDP (1.2 mg/kg × 5) resulted in a median survival (MS) of ca. 60 days vs <20 days in untreated controls, whereas the same schedule had no therapeutic effect on the survival of O-342/DDP-bearing rats (MS; 15 days in both DDP-treated and control groups (Zeller et al., unpublished results; a detailed description of the tumor model is in preparation). O-342/DDP cells have a higher intracellular reduced glutathione (GSH) level and a higher activity of GSH-reductase than their sensitive parental cells [15].

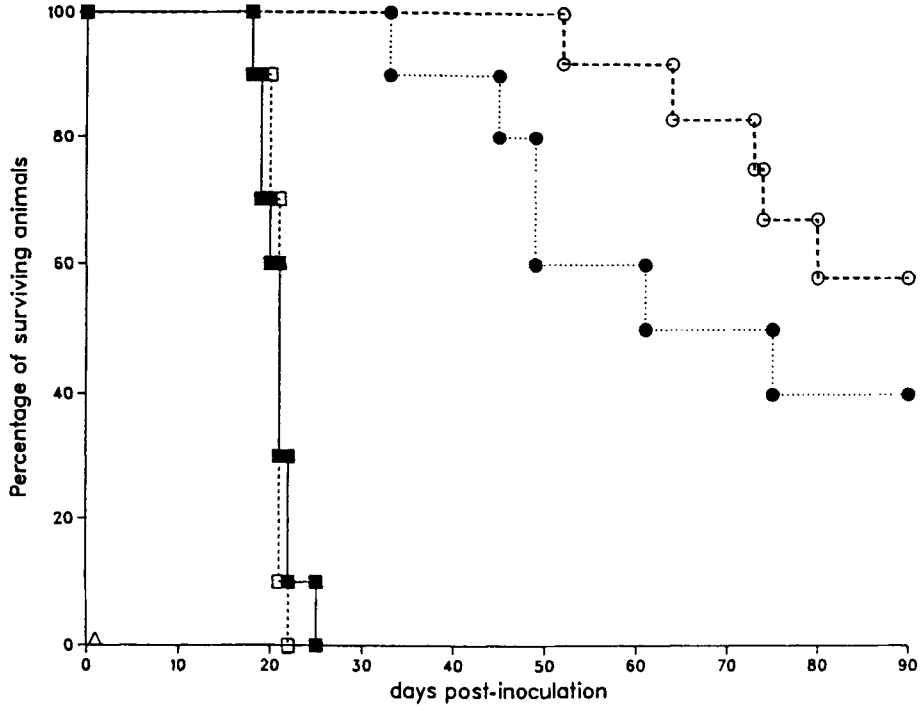

Fig. 1. Prolongation of survival in NMRI nude mice bearing intraperitoneal O-342 cells by 3-AB combined with DDP vs DDP alone. ■ (——), control; □ (– – –), 3-AB (5 m*M*/kg); ● (.....), DDP (1 mg/kg); ○ (– – –), DDP + 3-AB (schedule cf. Table 2)

Table 2. Potentiation of antitumor activity of DDP by 3-AB in the sensitive ovarian tumor O-342 in NMRI nude mice

Treatment[a]			Schedule	Survival (days):		S90[b]	ILS[c] (%)	*P*
0.9% saline	5 mM/kg 3-AB	1 mg/kg DDP		MS	Mean ± SD			
+	–	–	EOD, days 2–6	21	20.7± 2.1	0/10	–	–
+	+	–	EOD, days 2–6	21	20.6± 1.1	0/10	– 0.48	>0.05*
+	–	+	EOD, days 2–6	68	67.2± 22.4	4/10	224.6	<0.01*
–	+	+	EOD, days 2–6	90	81.1± 12.8	7/12	291.8	<0.01* <0.05**

[a] Drugs were simultaneously given i. p.
[b] Animals surviving for >90 days/ total No. of animals
[c] ILS (increase in life-span vs. untreated controls) = [(treatment – control)/control] × 100
* vs control; ** vs DDP alone; data treated with analysis of variance
EOD, every other day; MS, median survival

Both O-342 and O-342/DDP cell lines were maintained in BD IX rats by i. p. inoculation, with an interval of about 10–12 days.

Evaluation of antitumor activity. About 10^6 tumor cells were transplanted i. p. into NMRI female nude athymic mice. According to their weight, tumor-bearing mice were randomly divided into different groups. Therapy was initiated 24 or 48 h after inoculation. DDP was diluted in 0.9% saline or 3-AB-containing (36.2 mg/ml) 0.9% saline at a final concentration of 0.05 mg/ml. DDP and 3-AB were simultaneously given i. p. To evaluate the therapeutic effect, the mean survival of treated animals was compared with that of untreated controls and analysed using student's *t*-test. In addition, median survival and the percentage of increase in life span were calculated

Results

Reversal of DDP resistance in O-342/DDP by 3-AB

Table 1 shows in vivo results of combination therapy in the O-342/DDP tumor treated with DDP plus 3-AB. Six applications of 3-AB alone at a dose of 5 m*M*/kg had no therapeutic effect, yielding a mean survival of 23 days as compared with 23.8 days in the saline-treated control group. This is consistent with results reported thus far [10, 13]. Due to resistance, six doses of DDP (1 mg/kg each) were ineffective [increase in mean survival over that of controls, 1 day (ILS: 4.2%, $P > 0.05$)]. The combination of DDP plus 3-AB, on the other hand, resulted in a significant increase in survival compared with that achieved with DDP treatment alone (31% ILS; $P < 0.001$). This result was reproducible (data not shown).

Potentiation of antitumor activity of DDP by 3-AB in the sensitive ovarian tumor line O-342

Table 2 and Fig. 1 gives in vivo results of combination therapy using DDP plus 3-AB in the sensitive line O-342. As observed in the resistant tumor, 3-AB alone did not show a therapeutic effect. Treatment with DDP (1 mg/kg × 3) resulted in an increase in the mean survival of up to 67.2 days (median, 68 days) compared with 20.7 days (median, 21 days) in the control group. This underlines the high sensitivity of this rat ovarian tumor model to DDP treatment. The addition of 3-AB to the DDP regimen further increased the mean survival to 81.1 days. As shown in Table 2, the median survival in this combination-treatment group increased by 3 weeks over that in animals treated with DDP alone. Whereas the latter resulted in 4/10 cures (40%), the combination of DDP plus 3-AB achieved 7/12 cures (58%). The difference in mean survival between the combination-treatment group and the DDP group was significant ($P < 0.05$).

Discussion

The above results demonstrate that 3-AB can potentiate the antitumor activity of DDP in vivo in both the resistant line O-342/DDP and its sensitive parental counterpart O-342. The combination of 3-AB plus DDP prolongs survival in NMRI nude mice bearing O-342/DDP by about 1 week (31% ILS), whereas there is no response to DDP treatment alone; to our knowledge, this is the first report on the reversal of complete resistance to DDP by 3-AB in an ovarian tumor model in vivo, which appears to be encouraging, since effective methods to conquer drug resistance in tumor cells are urgently needed.

No increase in the toxicity of the combination vs that of DDP alone was observed. This is in agreement with our previous observations that 3-AB does not increase but rather reduces acute lethality and nephrotoxicity caused by DDP in mice, whereas the antitumor activity of DDP in sarcoma 180 and Ehrlich ascites carcinoma cells was potentiated by 3-AB in vivo, suggesting an inhibition of DNA repair by 3-AB [14]. Results from Umbach et al. [43], showing that 3-AB increases DDP cytotoxicity in murine fibrosarcoma cells but does not enhance it in human ovarian cancer cells in vitro, point out that in vitro and in vivo, human ovarian tumor lines, have to be included in further investigations to assess the potential of 3-AB in combination with DDP in this tumor type.

It is well known that DDP exerts its cytotoxicity by reacting with DNA, effecting DNA intrastrand and interstrand cross-links as well as DNA-protein cross-links; DNA interstrand cross-links are considered to play a key role in DDP cytotoxicity in many tumor cell lines [25].

Resistance to DDP in ovarian tumor cell lines is considered to be multicausal, including a decrease in the cellular uptake of DDP [3], an increase in DNA repair activity [19, 40], and an increase in cellular glutathione [15, 22] and/or in metallothioneines [4, 22]. Although the exact mechanism whereby 3-AB overcomes resistance to DDP remains to be elucidated, the following observations suggest that 3-AB probably reverses resistance to DDP by the inhibition or suppression of increased DNA repair activity:

1. 3-AB has been reported to inhibit DNA repair induced by various alkylating agents and 5-hydroxymethyl-2'-deoxyuridine [9, 41].
2. A reduced stimulation of poly (ADP-R)-synthesis was observed in a peplomycin-supersensitive lung cell line as compared with the parental lung cells following treatment with peplomycin [36], whereas a higher induction of poly(ADP-ribose) polymerase activity after bleomycin (BLM) treatment was recently reported in BLM-resistant Hela cells in which elevated DNA repair activity was found to play an important role in the development of BLM resistance [44, 45].
3. There is direct and indirect evidence that enhanced DNA repair may constitute one mechanism of resistance to DDP [19, 39, 40].
4. We observed a reduction in DNA interstrand cross-links in O-342/DDP cells compared with O-342 cells, probably due to enhanced DNA repair in the resistant cells [16]. Furthermore, our preliminary results indicate that 3-AB increases DNA single-strand breaks (SSB) and decreases DNA interstrand cross-links (ISCL) following treatment with DDP in O-342 and O-342/DDP cells (unpublished observations). An investigation on the significance of this finding as well as the determination of ADPRT activity in both cell lines following DDP treatment with or without 3-AB are presently under way in our laboratory.

Since in vivo tumors are considered to consist of heterogenous fractions of cells with differing sensitivity to a drug [31], there appears to be a gliding transition between sensitivity and resistance rather than a sharp borderline. In O-342/DDP, the fraction of completely resistant cells approaches unity, as indicated by the results obtained with DDP alone; nevertheless, 3-AB can significantly increase survival by 30% in this tumor. This potency of 3-AB can apparently very effectively overcome resistance – partial or complete – in a minor fraction of O-342 cells, such that the overall action of the 3-AB/DDP combination treatment appears to be more pronounced in the sensitive than in the resistant line with regard to survival. This result suggests that 3-AB could be a candidate for the treatment of early-stage ovarian cancer in combination with DDP to achieve a maximal therapeutic effect.

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