Combinations of single doses and fractionated treatments of cis-dichlorodiammineplatinum (II) and irradiation: Effect on mouse lip mucosa

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Summary  Tolerance of the lip mucosa of NMRI mice to single and fractionated irradiation combined with cis-diaminedichloroplatinum (II) (cis-DDP) was investigated. For the various combination schedules total drug doses varying from 6 mg kg\(^{-1}\) to 13 mg kg\(^{-1}\) were injected i.p. It was found that cis-DDP did not alter the radiation sensitivity of this tissue at any of the time intervals tested (ranging from 24 h before to 72 h after single dose irradiations).

When 5 daily drug injections were given concomitantly with 5 daily radiation treatments, a slight reduction of the lip mucosal reactions occurred, possibly due to partial synchronisation during treatment. No effect was seen when a single injection of cis-DDP preceded two irradiations given with increasing intervals up to 4 h. Both these combined fractionated treatment data suggest no inhibitory effect on repair of sublethal radiation damage.

When repeated daily injections of cis-DDP were given in between 2 radiation doses separated by 10 days, no interference with repopulation could be detected.

The present study also demonstrated an increase in systemic drug toxicity when cis-DDP was combined with irradiation, compared with that seen with either agent alone.

Cis-dichlorodiammineplatinum (II), (cis-DDP), is an antineoplastic agent used either alone and more recently in combination with other drugs for the treatment of a variety of malignancies, including testicular, ovarian, lung, bladder and head and neck tumours. In vitro studies with both normal and tumour cell lines suggested that cis-DDP acts as a modifier of radiosensitivity (Richmond et al., 1977; Douple & Richmond, 1980; Murthy et al., 1979; Dritschilo et al., 1979). Several studies with animal tumours also revealed enhancement of the radiation response when cis-DDP and irradiation were given at short time intervals (Douple & Richmond, 1982; Overgaard et al., 1981; Kyriazis et al., 1983; Höglmeier et al., 1985; Lelieveld et al., 1985).

An increasing number of clinical phase I-II studies has been carried out with combined treatments of radiotherapy and cis-DDP at varying dose schedules (Reimer et al., 1981; Keizer et al., 1984; Dewit et al., 1985; Pinedo et al., 1983). However, these data do not allow any firm conclusions as to the effect of cis-DDP in combination with radiotherapy on human normal tissues.

Attention has been drawn to increased acute normal tissue reactions due to the combined use of cancer chemotherapeutic agents with radiotherapy (Phillips et al., 1976; Peckham et al., 1981). Since the normal tissue tolerance is the limiting factor in the treatment of most malignancies, qualitative and quantitative knowledge of the possible interactions between cis-DDP and radiotherapy on normal tissues is necessary. In addition, information on the optimal dose and timing of cis-DDP in relation to irradiation is needed.

The present study reports on the effect of cis-DDP on the radiosensitivity as well as on repair of sublethal radiation damage and repopulation during fractionated radiotherapy in the lip mucosa of mice. This tissue was selected as a model for fast proliferating tissues (Ang et al., 1985).

Methods and materials

The experiments were carried out using 8 to 9 weeks old female Naval Medical Research Institute (NMR1) mice. These outbred mice were bred in specific pathogen free conditions and were transported to a conventional housing facility for treatment and follow-up. They were housed 6 per cage with free access to food and water.

Irradiations were delivered with a 60Co gamma-ray unit. The dose rate at a focus-to-skin distance of 60 cm was 170 cGy min\(^{-1}\) in some experiments and 140 cGy min\(^{-1}\) for others. With the use of a

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Results

Toxicity of cis-DDP alone and combined with irradiation

A series of experiments were carried out to assess toxicity of cis-DDP in the female NMRI mice following single and repeated i.p. injections. For single injection the drug dose needed to induce 50% lethality within a period of 30 days (LD50/30) was found to be 21 mg kg\(^{-1}\) in one experiment but later however, the LD50/30 was only 15 to 16 mg kg\(^{-1}\). When 5 i.p. injections of cis-DDP were given at 24 h-intervals, the LD50/30 was estimated to be \(\approx 21\) mg kg\(^{-1}\) total dose. The latter result was obtained at the same time period during which the first single injection study was carried out. In both schedules of drug administration, the maximum cis-DDP dose causing no lethality was 13–14 mg kg\(^{-1}\).

During the 30 days of observation, the body weight of all animals was recorded daily. The results showed no weight loss for a single injection of 6 mg kg\(^{-1}\) drug and \(\sim 12\%\) loss of body weight following a single treatment of 8 mg kg\(^{-1}\) cis-DDP. Weight loss after 10 and 13 mg kg\(^{-1}\) single injections varied from 10 to 25\% with relatively large individual variations between the mice. Slightly smaller changes in body weight were observed with the repeated daily injections when comparing the same total drug doses up to 10 mg kg\(^{-1}\). Following the decrease in body weight, the surviving mice however recovered to more than the initial weight within the observation period. Acute morbidity occurred between 5 and 9 days after drug injection and was always preceded by severe dehydration and dramatic loss of body weight. Macroscopically, the intestines were often swollen with a watery content. Histological preparations of the small intestine, resected immediately post-mortem, showed atrophied crypts and shortened villi.

Combining cis-DDP with irradiation, at any of the doses used, led in a number of experiments to a more pronounced loss of body weight than expected from the sum of weight loss of both agents alone (Table I). The decrease was observed at the time period of the maximal lip mucosal reaction and persisted for several days. The phenomenon of a greater reduction in body weight was more obvious in fractionated compared with single treatments.

Combined cis-DDP and irradiation: lip mucosal reactions

Figure 1 shows the results of two time-line experiments combining 8 mg kg\(^{-1}\) (A) or 13 mg kg\(^{-1}\) (B) single i.p. cis-DDP injections with a single radiation dose of 15 Gy.

The drug administered at either 24 h, 6 h, 2 h, 15 min before or 15 min, 2 h, 6 h, 24 h, 72 h after the irradiation.

No enhancement of the lip mucosal reactions was recorded at any of the time-intervals used. In fact,
cause an desquamation
probably implicate
DDP

This corresponds to
following (± s.e.)

8 mg
15 Gy (dose
1.4 Gy min−1).

a

and oedema
reduced.

Figure 1 Time-line experiments using a single i.p.
injection of cis-DDP given at various time intervals
before and after a single radiation treatment. (A) 8 mg kg−1
drug combined with 15 Gy (dose rate of
140 cGy min−1). (B) 13 mg kg−1 drug combined with
15 Gy (dose rate of 170 cGy min−1). The hatched area

In Figure 2 (A and B), the dose-response curves
obtained after single irradiation alone and after i.p.
injection of 13 mg kg−1 cis-DDP 2 h prior to single
irradiation doses, confirm the above mentioned
findings. The reduction in the reaction score
following combined treatment (Figure 2A) is not
significant when the scores for oedema are excluded
(Figure 2B). Also the percentage of animals
showing focal desquamation of the mouse lip
mucosa were similar for both treatment modalities
(Table II).

Results of the investigation of a possible
influence of cis-DDP on the extent of repair of
sublethal radiation damage are presented in Figure 3.
Fractionated, daily treatment of irradiation and
cis-DDP (1.2 or 1.6 mg kg−1 given 30 min before
each irradiation) for 5 consecutive days resulted in
less radiation damage compared with irradiation
alone (Figure 3A), even when the oedema scores
were not used for calculating the mean peak
reactions (Figure 3B). Reduced reactions were not only
observed at the day of peak reactions but were
found over the whole reaction course after the
combined treatment. The lower incidence of spotted
desquamation in the mouse lip following the
concomitant use of cis-DDP and irradiation is
demonstrated in Table II.

Experiments combining cis-DDP and two
radiation doses given with increasing fractionation
intervals (1 to 4 h) were done to assess the possible
influence of cis-DDP on the rate of repair of
sublethal radiation damage. The results did not

Figure 1 shows that slightly less lip mucosal re-
actions occurred after the concomitant use of cis-
DDP and irradiation. However, this does not
necessarily implicate a protective effect and most
probably was the result of the often occurring
dehydration of the cis-DDP treated animals leading
to a reduced oedema score. This would obviously
cause an underestimate of the total score relating to
the acute lip mucosal reactions; the erythema and
desquamation scores were not significantly altered.

### Table I Maximum weight loss for various treatment modalities.

| Irradiation | Total dose (Gy) | cis-DDP (mg kg−1) | %Max. weight loss (± 1 s.e.) |
|-------------|----------------|------------------|-----------------------------|
| Scheme      | 1 × 8          | 12.2 ± 2.1       |                             |
|             | 1 × 13         | 19 ± 2           |                             |
|             | 5 × 1.2        | 0                |                             |
|             | 5 × 1.6        | 5 ± 2            |                             |
|             | 5 × 2.0        | 2.7 ± 1.3        |                             |
| 1F          | 14.5           | 1 × 8            | 7.8 ± 2.5                   |
|             |                | (2 h prior RT)   |                             |
| 1F          | 14.5           | 1 × 13           | 29.8 ± 3.7                  |
|             |                | (2 h prior)      |                             |
| 5 daily F   | 28             | 5 × 1.2          | 10.5 ± 2.9                  |
|             |                | (30 min prior RT)|                             |
| 5 daily F   | 28             | 5 × 1.6          | 25.3 ± 4                    |
|             |                | (30 min prior RT)|                             |
| 5 daily F   | 28             | 5 × 2            | >35*                        |
|             |                | (30 min prior RT)|                             |

*aSacrificed after body weight measurement.*
Figure 2 Dose-response curves representing the mean peak mucosal reactions as a function of administered radiation dose. Cis-DDP (13 mg kg\(^{-1}\)) is injected i.p. at 2 h prior a range of single radiation doses. Calculations were accomplished including the oedema score (A) or without the oedema score (B). ○: irradiation alone, ●: combined treatment.

Table II Percentages of animals showing focal desquamation of the mouse lip mucosa after irradiation alone or after irradiation combined with i.p. cis-DDP administration.

| Dose (Gy) | % Incidence (without cis-DDP) | % Incidence (with cis-DDP)\(^{a}\) | % Incidence (without cis-DDP) | % Incidence (with cis-DDP)\(^{b}\) |
|-----------|------------------------------|-------------------------------|------------------------------|-------------------------------|
| 14.5      | 0                            | 0                             | 28.0                         | 0                             |
| 16.0      | 33                           | 25                            | 29.5                         | 0                             |
| 17.5      | 83.5                         | 100                           | 31.0                         | 0                             |
| 19.0      | 100                          | 100                           | 32.5                         | 67                            |

\(^{a}\)Drug administered 2 h prior to irradiation; \(^{b}\) each drug administration 30 min prior to each irradiation.

indicate any influence of the drug on the repair kinetics (data not shown) when the drug was injected 30 min prior to the first radiation treatment.

The effect of cis-DDP on repopulation, 5 daily drug injections were given during the interval between both fractions using either 1.2 mg kg\(^{-1}\) or 1.6 mg kg\(^{-1}\) cis-DDP to total doses of 6 mg kg\(^{-1}\) or 8 mg kg\(^{-1}\) respectively. The injections were given daily starting at day 3 after the first irradiation. The reaction curves (total radiation dose of 19 Gy) shown in this figure demonstrate clearly that the addition of repeated drug injections did not alter
The response of the mouse lip mucosa to 5 equal radiation doses separated by 24 h without cis-DDP (○) and with 5 daily i.p. injections of either 1.2 mg kg\(^{-1}\) (●) or 1.6 mg kg\(^{-1}\) (■) drug at 30 min interval. The dose response curves of part A are constructed including the oedema scores, while in part B the oedema scores are omitted.

Course of mouse lip mucosal reactions following 2 equal radiation doses of 14.5 Gy each at 10 days interval. The average reaction includes the oedema score and is plotted as a function of time after the first radiation treatment. The various schedules are: Irradiation alone (○); Irradiation with 1.2 mg kg\(^{-1}\) (▲) or 1.6 mg kg\(^{-1}\) (■) cis-DDP given daily i.p. from 3 to 7 days after the first radiation exposure.
the course of radiation responses. Similar results were also obtained for the lower radiation doses used.

Discussion

Toxicity

Our histological findings are in agreement with the marked intestinal cytotoxicity described earlier in rats and mice (Choie et al., 1981; Kovacs et al., 1982; Luk et al., 1979; Schaeppi et al., 1973). Obviously, the rapidly developing acute renal damage with cis-DDP doses of more than 6 mg kg\(^{-1}\) (Stewart et al., 1986) will add to the observed body weight loss and eventual lethality.

The results from our cis-DDP toxicity studies with the NMRI mice showed LD\(_{50/30}\) variations for single i.p. injections. It was also noticed that the responses to the drug were subject to individual variations within one dose group. This is true for every group of mice receiving the same amount of cis-DDP. Investigations on kidney function in mice after cis-DDP administration showed a similarly broad range of individual acute responses at doses above 6 mg kg\(^{-1}\) (Stewart et al., 1986).

When the drug was combined with irradiation a more pronounced body weight loss occurred, also at the lowest radiation and drug doses used. This increased toxicity following the combined irradiation and cis-DDP treatment, as compared to the sum of both agents alone, was also reported by others (F. Stewart & L. Dewit, personal communication) and was found previously with other drugs, i.e. actinomycin D (Landuyt et al., 1985) and methotrexate (von der Maase, 1984). This is probably the result of a spatial combination of normal tissue toxicity, an assumption based on the fact that evidence for systemic toxicity and lip mucosal injury showed a similar onset in time.

Combined cis-DDP and irradiation: lip mucosal reactions

The results of our time-line experiments, in which a single injection of cis-DDP was given at various time intervals from 1 day before to 3 days after a single radiation exposure, showed no clear modifications of the radiation induced lip mucosal damage. Neither was there any evidence of modified radiation damage when a fixed amount of drug was delivered before or after a range of radiation doses. It was also demonstrated that the reduced scores, due to the administration of cis-DDP and occurring in some combined schedules, were probably the result of dehydration of the animals. Since this phenomenon leads to a reduced swelling of the lips, omission of the oedema score shows that only minor differences existed between both combined treatment and radiotherapy alone. The incidence of spotted desquamation in the mouse lip after radiation treatment was not modified with the use of cis-DDP. These results therefore illustrate that the radiosensitivity of this rapidly proliferating tissue does not seem to be affected by cis-DDP for both the time intervals and sequences used.

In agreement with this finding, absence of interaction between radiation and cis-DDP on the skin of mouse foot has been previously reported (Overgaard et al., 1981; Lelieveld et al., 1985). Some investigators, however, did show a moderate increase of skin reactions in mouse foot (von der Maase, 1984) as well as in the rat foot (Doupe et al., 1979). A phase I/II clinical study combining radiotherapy and daily low dose cis-DDP for treatment of locally advanced cancers showed no clear increase of the oral mucosal reactions or skin lesions (Keizer et al., 1984). Other clinical data also indicated no change of radiation induced acute skin reactions when cis-DDP was given concurrently with radiotherapy for treatment of solid tumours (Dewit et al., 1985a; Reimer et al., 1981). In contrast, a number of studies showed enhancement of radiation damage in the intestinal mucosa of mice when cis-DDP was given i.p. at various time periods before or after single radiation exposure (Luk et al., 1979); von der Maase, 1984). However, the effect only occurred when the drug dose exceeded 6 mg kg\(^{-1}\). An enhancement of acute radiation damage to the small intestine in patients has also been shown to be cis-DDP dose dependent (Dewit et al., 1985a).

No interaction of cis-DDP with the extent nor the kinetics of repair of sublethal radiation damage was demonstrated in the present study. It was actually found that, following a combined treatment of 5 daily cis-DDP injections given 30 min before 5 daily irradiations, the lip mucosal reactions were consistently lower compared with those after radiotherapy alone. This small but significant protective effect could not be explained by dehydration since exclusion of the oedema scores from the calculation of mean peak level of mucosal reaction did not eliminate this phenomenon. These effects may be explained partly by synchronisation occurring during the treatment course. These results on mouse lip mucosa are in agreement with the data of Bartelink et al. (1983) and Lelieveld et al. (1985) on mouse skin, demonstrating no modification of the capability to repair sublethal radiation damage. While inhibition of repair of sublethal radiation damage by cis-DDP has been suggested in several investigations on
mouse intestinal epithelium (Dewit et al., 1985b, Bartelink et al., 1983; Burholt et al., 1979), no such effect was measured when low dose rate irradiation was combined with continuous i.p. infusion of cis-DDP using the same biological model (Fu et al., 1984).

Finally, the possible interference of cis-DDP with repopulation during fractionated irradiation was also investigated. Our data do not show any influence of fractionated drug treatments (6 or 8 mg kg\(^{-1}\) total dose) on the repopulation capacity of mouse lip mucosa. Figure 4 illustrates the results obtained with a total radiation dose of 29 Gy, but similar results were obtained for lower radiation doses. Higher cis-DDP doses could not be tested, since in this combined treatment they always resulted in very severe toxicity and subsequent lethality.

In conclusion, these data on lip mucosa do not show an increase of the radiosensitivity nor an inhibition of repair at the cellular or tissue level. On the contrary, they indicate a minor protection (6-9%) dependent on the fractionation schedule used. Thus it follows from our results and from data in the literature that the effect of cis-DDP on radiation treatment is strongly dependent on the type of tissue involved. It also seems clear that large combined effects are apparent in intestinal mucosa when high drug doses are used. This could be related to the fact that at these doses of cis-DDP a marked independent cell killing in gut mucosa occurs from the drug alone.

There certainly remains a need for more data derived from the combination of fractionated drug and radiation treatments used concomitantly as well as alternately in a variety of normal and tumour tissues, to define the optimal use of combined modalities in clinical practice.

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