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# INTERACTIONS OF RADIATION AND CANCER CHEMOTHERAPEUTIC DRUGS IN A C3H MOUSE MAMMARY CARCINOMA

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**Abstract**

The interactions of radiation and adriamycin (ADM), bleomycin (BLM), cyclophosphamide (CTX), 5-fluorouracil (5-FU), methotrexate (MTX), mitomycin C (MM-C), or cis-diamminedichloroplatinum II (cis-DDP) were studied in a spontaneously arisen C3H mouse mammary carcinoma. The tumour response to drugs alone was evaluated by measuring the tumour growth time defined as the time required for a tumour to reach a volume 5 times that of the treatment day. CTX resulted in a marked tumour growth delay whereas the other drugs had a modest or uncertain effect. In the combined treatment experiments, drugs were administered as single doses either 15 min before or 4 hours after graded single doses of irradiation. The end point for each treatment was the radiation dose which on an average was required to achieve local tumour control in 50 per cent of the mice ($TCD_{50}$). The dose effect factor (DEF) was 1.16 for ADM and 1.17 for CTX, the enhanced radiation response being independent of administration before or after irradiation. MM-C also decreased the $TCD_{50}$ for radiation alone, but its effect was more marked 15 min before (DEF 1.32) than 4 hours after irradiation (DEF 1.18). BLM, 5-FU, MTX, and cis-DDP had no effect on the radiation response neither when administered 15 min before nor 4 hours after irradiation.

Despite the frequent application of radiation in combination with cancer chemotherapeutic drugs, knowledge on the interactions of these two treatment modalities is still limited. We have previously studied drug-radiation interactions in mouse intestinal tract mucosa (20, 22, 23), in mouse foot skin (21), and studies on the interactions in haematopoietic tissue and lung are ongoing. The present work continues along the line of these studies, and its aim was to evaluate the effects of radiation alone and in combination with adriamycin, bleomycin, cyclophosphamide, 5-fluorouracil, methotrexate, mitomycin C, or cis-diamminedichloroplatinum II in a solid tumour system.

## Material and Methods

### *Animal tumour system*

All experiments were carried out with 9 to 12 weeks old male $C_3D_2F_1$/Bom mice ($C_3H$/Tif♀ × DBA/2♂). They were housed 2 per cage and given standard laboratory diet and water ad libitum. The mice were challenged with a spontaneously arisen C3H/Tif mammary carcinoma propagated by serial transplantation. Tumour material for inoculation was obtained by sterile dissection of large flank tumours. Macroscopically viable tumour tissue was minced with a pair of scissors, and 5 to 10 µl was injected into the foot of the right hind limb of the animals. The transplant take was about 99 per cent. Tumours reaching a volume of approximately 200 $mm^3$ (determined by the $\pi/6 \times D1 \times D2 \times D3$ formula in which the Ds are 3 orthogonal diameters) within 12 to 24 days of inoculation were used for treatment (16).

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*Irradiation*

Unanaesthetized mice were placed in Lucite jigs with the tumour-bearing leg loosely fixed with tape without impairing the blood flow to the foot (25). The tumour-bearing leg was immersed in a water bath and treated with single radiation doses whereas the remaining part of the mouse being shielded by 1 cm lead sheets (21). Radiation treatment was delivered by a 250 kV Müller roentgen unit (15 mA, filtration 2 mm Al, HVL 1.1 mm Cu, dose rate 3.25 Gy/min).

*Drugs*

The investigated drugs were adriamycin (ADM), bleomycin (BLM), cyclophosphamide (CTX), 5-fluorouracil (5-FU), methotrexate (MTX), mitomycin C (MM-C), and cis-diamminedichloroplatinum II (cis-DDP).

For each drug estimation was made of the maximum tolerated dose (MTD), i.e. the dose that would kill approximately one per cent of the mice within 150 days (21). BLM was dissolved in sterile isotonic saline and the other drugs in sterile distilled water. All drugs were administered intraperitoneally as single doses at a constant volume of 0.02 ml/g of body weight.

*Evaluation of data*

*Tumour growth time.* After treatment with single doses of drug alone, the tumour volume was measured daily. The tumour response was evaluated as the tumour growth time, i.e. the time required for a tumour to reach a volume 5 times that of the treatment day. The exponential regrowth phase was evaluated as the tumour doubling time. All calculations were based on growth curves for each individual mouse. Each experiment included 8 to 10 mice per drug and was reproduced at least once.

*Local tumour control.* The effect of graded doses of radiation alone and in combination with drugs was evaluated by calculation of the radiation dose which on an average was required to achieve local tumour control in 50 per cent of the mice ($TCD_{50}$). The animals were followed up every 3 to 4 weeks and tumour control was defined as absence of macroscopically detectable local relapse for 120 days. Mice dying within this period without evidence of tumour were excluded from the evaluation.

All experiments included 6 to 10 mice per dose point and were reproduced at least once. Dose response curves were based on at least 5 dose points. In most of the 4-hour interval experiments only representative points and not full dose response curves were reproduced. The $TCD_{50}$ values, based on the pooled data, were computed by a logit analysis (41). A standard $\chi^2$-test was used for statistical analysis. The drug-radiation interactions were estimated by the dose effect factor (DEF),

$$\text{DEF} = \frac{\text{TCD}_{50} \text{ for radiation alone}}{\text{TCD}_{50} \text{ for radiation + drug}}$$

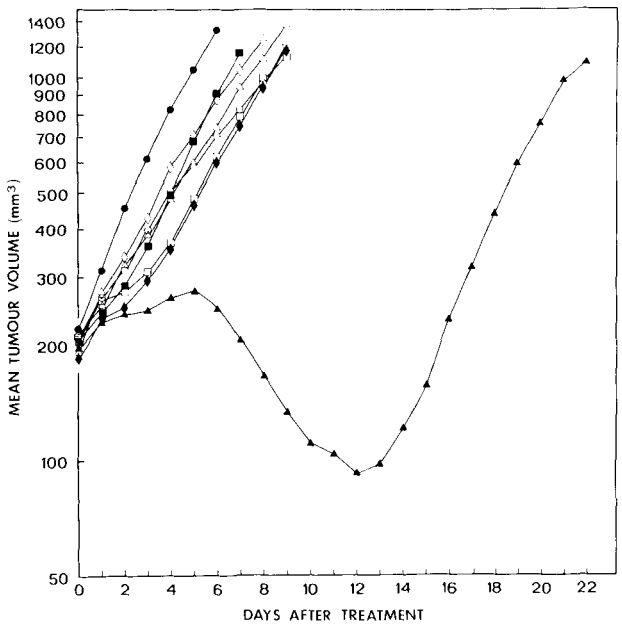


Fig. 1. Tumour growth curves for untreated controls and cases treated with drugs alone. Points represent mean volume of 16 to 36 tumours (Table 1). Control (●), ADM (○), BLM (△), CTX (▲), 5-FU (□), MTX (■), MM-C (◇), cis-DDP (◆).

**Table 1**

*Tumour growth time and tumour doubling time after treatment with drugs alone. All calculations were based on growth curves for each individual mouse. Mean growth curves are shown in Fig. 1. Number in parentheses, 95% confidence limits*

| Treatment | No. of mice | Tumour growth time (days) | Tumour doubling time (days) |
|---|---|---|---|
| Untreated controls | 36 | 5.3 (5.0–5.6) | 2.4 (2.2–2.6) |
| ADM 8 mg/kg | 34 | 8.5 (7.7–9.3) | 3.9 (3.4–4.4) |
| BLM 100 mg/kg | 17 | 8.1 (7.6–8.6) | 3.4 (2.9–3.9) |
| CTX 100 mg/kg | 16 | 20.6 (19.4–21.8) | 2.5 (2.1–2.9) |
| 5-FU 150 mg/kg | 22 | 8.7 (7.5–9.9) | 3.1 (2.9–3.3) |
| MTX 150 mg/kg* | 31 | 6.8 (6.3–7.3) | 2.6 (2.2–3.0) |
| MM-C 3 mg/kg | 29 | 7.1 (6.3–7.9) | 3.5 (3.1–3.9) |
| Cis-DDP 6 mg/kg | 31 | 7.9 (7.3–8.5) | 2.7 (2.4–3.0) |

* MTX dose = $\frac{1}{5}$ MTD; other drug doses = MTD.

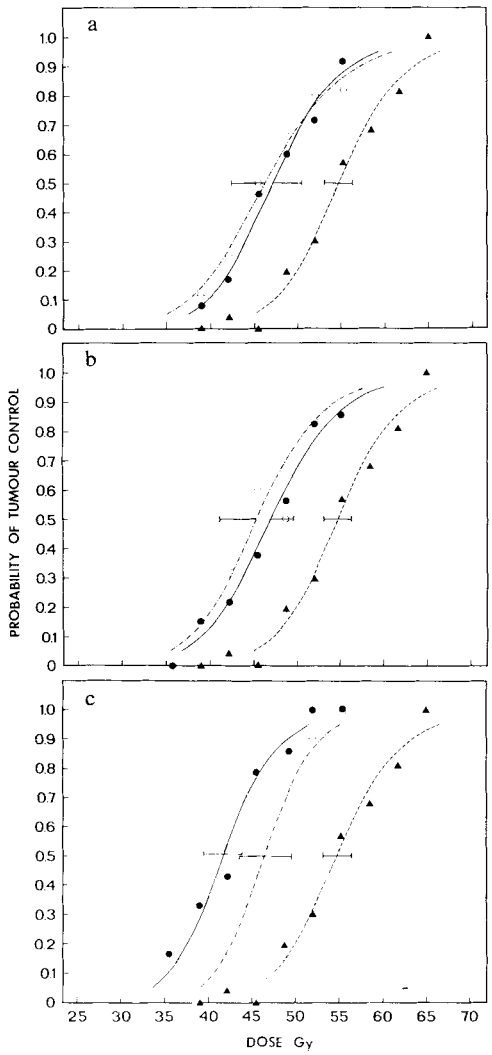


Fig. 2. Dose response curves for radiation alone (▲) and for irradiation combined with drugs administered either 15 min before (●) or 4 hours after (○) irradiation. Bars represent 95% confidence limits. $TCD_{50}$ values are given in Table. 2. a) ADM, b) CTX, c) MM-C.

## Results

*Drugs alone.* The MTDs of single drug doses are given in Table 1. As previously described for drug-radiation interactions in mouse foot skin it was not possible to use the MTD of MTX (750 mg/kg) and instead a dose of 150 mg/kg (1/5 MTD) was administered (21). All other drugs were administered at the MTD.

The tumour response to drugs alone was studied by measuring the tumour growth time. As seen in Fig. 1 treatment with CTX resulted in a marked tumour growth delay. The tumour growth time was increased by a factor of 3.9 without changing the tumour doubling time (Table 1). Treatment with the other drugs alone revealed minor but statistically significantly increased tumour growth times (Table 1). For MTX and cis-DDP, the increased tumour growth time was obtained without significantly changing the tumour doubling time, whereas both ADM, BLM, 5-FU and MM-C also increased the tumour doubling time (Table 1).

*Drug-radiation combinations.* The drug-radiation interactions were studied by administration of drugs either 15 min before or 4 hours after graded radiation doses. The drugs were administered 4 hours after irradiation as repair of sublethal radiation damage was expected to have been completed within this period.

The dose response curves for ADM administered 15 min before and 4 hours after irradiation are compared with that for radiation alone in Fig. 2a. ADM statistically significantly decreased the $TCD_{50}$ which gave a DEF of 1.16 and 1.18 at the two intervals (Table 2). Similarly, CTX significantly enhanced the radiation response when administered either 15 min before or 4 hours after irradiation, the DEF being 1.17 and 1.21, respectively (Fig. 2b, Table 2). As seen in Fig. 2c MM-C also decreased the $TCD_{50}$ at both intervals, but its effect was more marked ($p<0.05$) at administration 15 min before than 4 hours after irradiation. The DEF values at these two drug-radiation intervals was 1.32 and 1.18, respectively (Table 2). The effect of MM-C was also investigated at administration 6 hours before irradiation revealing an effect similar to that obtained at administration 15 min before irradiation.

The remaining four drugs, BLM, 5-FU, MTX and cis-DDP had no effect on the radiation response neither when administered 15 min before nor 4 hours after irradiation (Table 2). The effect of BLM, MTX and 5-FU was also investigated on administration 2 hours before, 1 hour before, and 6 hours after irradiation, respectively, as previous findings have revealed these drugs to enhance the radiation response in the intestinal tract epithelium to the largest extent at specifically these intervals (20, 22). However, the effect of the drugs administered at these intervals did not differ in any of the cases from the one obtained at the 15 min interval.

## Discussion

From a clinical point of view, tumour control is the most relevant end point for evaluation of drug-radiation combinations. In the present study only local tumour control could be evaluated due to the

negligible frequency of metastases within the observation period (120 days). The effect of the drugs alone was assessed by the tumour growth time as local tumour control was not obtainable for the single drug doses administered. However, the effect of the drugs alone may also be estimated from their effect at administration 4 hours after irradiation as this interval exceeds the period in which repair of sublethal radiation damage is expected to take place. Thus, according to the $TCD_{50}$ experiments, the effect of ADM, CTX and MM-C was almost the same (Fig. 2, Table 2). Inversely, according to the tumour growth experiments, only CTX had a marked effect by itself as opposed to ADM and MM-C which had an uncertain and in any case a modest effect (Fig. 1). The remaining four investigated drugs did not decrease the $TCD_{50}$, but the effect on the tumour growth time was more or less equivalent to that of ADM and MM-C. These apparent discrepancies between the two systems may reflect that the correlation between tumour growth delay and the killing of tumour cells may vary from drug to drug. Factors such as the host response, delayed cell proliferation and changes in the doubling time of surviving tumour cells may contribute to these differences (5, 40, 44). Injuries in the local stroma may also influence the tumour growth (1, 2, 53). It is furthermore important for the outcome of the combined treatments whether the drugs have killed a proportion of well-oxygenated radiosensitive cells or a fraction of hypoxic radioresistant cells. Thus, MM-C has been shown to be more toxic to hypoxic than aerobic cells in vitro (17, 27, 33, 43). This possible preferential killing of hypoxic tumour cells may be attributed to the effect of MM-C in combination with radiation treatment and may thus explain the apparent lack of a relationship between the two end points.

ADM decreased the $TCD_{50}$ for radiation alone to the same extent at administration 15 min before and 4 hours after irradiation which may indicate that the two treatment modalities may have an additive effect. The possible additive effect of the combined ADM and radiation treatment is in accordance with observations made in other studies both on tumour cells in vitro (6, 7, 14) and on solid tumours in vivo (13, 34, 42, 45). On the other hand, DETHLEFSEN & RILEY (9) have shown that ADM decreased the effect of radiation alone when administered 24 hours before irradiation of a slowly growing tumour and 96 hours before irradiation of a fast growing tumour.

**Table 2**

*Dose effect factors for drugs administered 15 min before and 4 hours after graded radiation doses. Number in parentheses, 95% confidence limits*

| Treatment | No. of mice | $TCD_{50}$ (Gy) | DEF* |
|---|---|---|---|
| Radiation alone | 188 | 54.79 (53.20–56.43) | – |
| ADM 15 min before radiation | 78 | 47.13** (44.36–50.08) | 1.16 |
| ADM 4 hours after radiation | 54 | 46.25** (42.40–50.45) | 1.18 |
| BLM 15 min before radiation | 94 | 53.07 (50.74–55.51) | 1.03 |
| BLM 4 hours after radiation | 56 | 52.65 (50.29–55.11) | 1.04 |
| CTX 15 min before radiation | 96 | 47.01** (44.52–49.64) | 1.17 |
| CTX 4 hours after radiation | 42 | 45.39** (41.21–49.99) | 1.21 |
| 5-FU 15 min before radiation | 56 | 56.08 (53.73–58.53) | 0.98 |
| 5-FU 4 hours after radiation | 41 | 55.73 (51.99–59.73) | 0.98 |
| MTX 15 min before radiation | 128 | 54.75 (51.46–58.24) | 1.00 |
| MTX 4 hours after radiation | 84 | 55.39 (52.91–57.98) | 0.99 |
| MM-C 15 min before radiation | 89 | 41.63** (39.43–43.95) | 1.32 |
| MM-C 4 hours after radiation | 48 | 46.41** (43.46–49.56) | 1.18 |
| Cis-DDP 15 min before radiation | 132 | 54.19 (51.34–57.19) | 1.01 |
| Cis-DDP 4 hours after radiation | 42 | 52.46 (48.80–56.40) | 1.04 |

* DEF: Dose effect factor $= \frac{TCD_{50} \text{ for radiation alone}}{TCD_{50} \text{ for radiation+drug}}$.

** Statistically significantly different from radiation alone ($p<0.001$).

The contradictory nature of these observations makes it desirable that further studies look into the importance of the intervals of ADM and radiation treatment.

The combined effect of CTX and irradiation could probably also be described as additive which is in agreement with most other tumour studies (15, 42, 46, 52). BEGG et coll. (3) also found an additive

effect although potentiation was observed at certain drug-radiation intervals, i.e. 1 and 8 hours after irradiation. In these studies and in the present work, interactions in the local tumours were evaluated, but it should be emphasized that the clinical problem generally is to control both the local tumour and the development of distant metastases. Thus, the objective of combining radiation and drugs is frequently to achieve a so-called spatial cooperation of the two treatment modalities (37, 38). Examples of a therapeutic gain obtained by spatial cooperation have been given by STEEL et coll. (39), CHU & FOWLER (8) and LOONEY et coll. (19). In these studies, CTX not only increased the local tumour control when combined with irradiation but also reduced the metastatic dissemination. In the study by CHU & FOWLER (8) the highest cure rate was obtained on simultaneous administration of CTX and irradiation.

MM-C enhanced the tumour response to the largest extent at administration 15 min before irradiation (Fig. 2 c). Similarly, ROCKWELL (31) found that in the EMT6 mouse mammary tumour MM-C was more effective when given before or immediately after irradiation than if administered 2 to 12 hours after irradiation. A similar dependence on the drug-radiation intervals was also obtained in mouse foot skin (21) and intestinal tract epithelium (22). The effect pattern may possibly indicate that MM-C hampers the repair of sublethal radiation damage. However, other studies on interactions of MM-C and irradiation both in vitro and in vivo have concluded that the two treatment modalities act in an additive manner and do not interfere with the repair of sublethal radiation injury (27, 30–32, 36). The decreased effect of MM-C administered 4 hours after irradiation may also be attributed to reoxygenation of hypoxic tumour cells within a few hours of irradiation as MM-C, as previously mentioned, has been shown to be more toxic to hypoxic than to aerobic cells. At present, we are planning more studies on the dependence on the intervals and sequence of the two treatment modalities.

The four remaining drugs BLM, 5-FU, MTX and cis-DDP did not change the $TCD_{50}$ for radiation alone (Table 2). This was especially surprising for BLM and cis-DDP which in our laboratory previously have been shown to enhance the radiation response in the C3H mouse mammary carcinoma used in the present study (24, 26). For BLM, the reason for the discrepancy may be that the tumour was then, as opposed to now, found to be sensitive to BLM as evidenced by an increased tumour growth time and no concomitantly decreased tumour doubling time (24). URANO et coll. (50) have also shown that BLM decreased the $TCD_{50}$ for radiation alone in a C3H mammary carcinoma. This tumour was also sensitive to BLM alone (49). However, in three BLM resistant solid tumours no significant effect on the radiation response was observed (48). Nor was BLM found to increase the effect of radiation alone in an EMT6 mammary carcinoma (4). Thus, the effect of BLM on the radiation response is probably dependent on the effect of BLM alone.

For cis-DDP, OVERGAARD & KHAN (26) observed a marked enhancement of the radiation response at administration 30 min before irradiation. Therefore, the effect of cis-DDP was also investigated at this interval in the present study, but the combined effect was still similar to that of radiation alone (data not shown). In the study by OVERGAARD & KHAN (26) it was suggested that cis-DDP had a radiosensitizing effect as also suggested in other studies (10–12, 28, 29). As opposed to the present study, OVERGAARD & KHAN (26) also found an effect of cis-DDP alone as assessed by the effect at drug administration 4 hours after irradiation. This difference, however, does not explain the present absence of evidence of a radiosensitization which should be independent of the effect of the drug alone. Nor did TWENTYMAN et coll. (47) observe any evidence of a radiosensitizing effect of cis-DDP in the treatment of three solid tumours. In two of the tumours the combined effect was probably additive whereas in the third tumour the effect may have been less than additive. The combination of cis-DDP and irradiation has also been experimentally investigated in bladder carcinoma (18, 35, 51). In these studies, the combined effect was more pronouncd than that of either treatment alone although it probably could not be attributed to a radiosensitizing effect. Thus, the mechanisms of the interactions of cis-DDP and irradiation seem far from sufficiently clarified.

The apparent change in the sensitivity of the C3H mammary carcinoma to BLM and cis-DDP emphasizes the importance of a continuous control of the tumour characteristics. During the 2-year period covered by the present study changes in the tumour growth time or the sensitivity to irradiation and drugs were not observed.

In conclusion, in the solid tumour system only three of the seven investigated cancer chemotherapeutic drugs enhanced the radiation response. As the modification of the radiation response seemed to depend mostly on the effect of the drugs alone, the outcome of the combined treatments may have been different if a tumour more sensitive to drugs alone was used. It should also be emphasized that the obtained drug-radiation interactions were based on single-dose experiments, and that the radiation-modifying effect of the drugs probably would have been more marked in a fractionated treatment schedule.

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