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# The Treatment of Advanced Bladder Cancer with Methotrexate and *cis*-Platinum—a Pharmacokinetic Study*

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**Abstract**—*As part of a phase III study in advanced bladder cancer, 5 patients received methotrexate (MTX) 50 mg/m² as a single agent every 2 weeks, and with every alternate dose of MTX (i.e. every 4 weeks) cis-platinum (CDDP) 50 mg/m² was given simultaneously, together with saline hydration and diuresis. The clearance of MTX was measured in a total of 12 courses by serial serum sampling for up to 72 hr following injection. In 4 patients (with a mean pretreatment creatinine clearance of 97 ml/min) there was no significant difference between the clearance of MTX when given alone [mean t½ (β) 3.2 hr] and when given 2 weeks later with concurrent CDDP [mean t½ (β) 2.9 hr]. In 1 patient with a pretreatment creatinine clearance of 52 ml/min the clearance of MTX when given alone (without hydration) was significantly delayed compared with the clearance of MTX when given 2 weeks later concurrently with CDDP and saline hydration [t½ (β) 19 and 4.5 hr respectively]. Of the 5 patients so far treated with MTX-CDDP, 2 have had a partial objective response and 3 have had stable disease (including 2 with a marked subjective response). These data indicate that in patients with satisfactory renal function, low-dose MTX and CDDP may be given concurrently without risk of enhanced drug toxicity.*

## INTRODUCTION

CLINICAL trials currently indicate that for the treatment of advanced bladder cancer, two of the most effective cytotoxic drugs are methotrexate (MTX) and *cis*-platinum (CDDP) [1]. Response rates of 30–40% have been noted for both these agents, and both have been introduced separately as single agents into trials of adjuvant chemotherapy in $T_3$ bladder cancer [2, 3]. The combination of MTX and CDDP might reasonably be expected to be more effective than either drug given alone, and clinical studies of this combination in advanced bladder cancer are in progress.

The theoretical disadvantage to the combination of these two potentially nephrotoxic agents is the risk of enhanced drug toxicity, particularly of MTX, if renal excretion of the drug were delayed by tubular damage resulting from concurrent CDDP therapy.

In order to ascertain, under carefully controlled conditions, whether MTX excretion might indeed be affected in this way, this study was carried out in patients with advanced bladder cancer and satisfactory pretreatment renal function, using each patient as his own control.

## MATERIALS AND METHODS

### *Patients*

The patients reported in this study were all male, aged 55–67 yr (mean age 60 yr). All had advanced or recurrent bladder cancer, with progressive disease following radiotherapy in 4 cases and total cystectomy in 2 cases. Sites of malignant disease were lymph nodes (2 cases), bone (3 cases) and bladder (1 case). All patients had satisfactory pretreatment renal function (see Table 1).

### *Treatment protocol*

On day 1 MTX was given as an intravenous bolus at the dose of 50 mg/m² without hydration.

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*Table 1. Pretreatment renal function and pharmacokinetic data on 5 patients when given MTX alone and when given MTX/CDDP*

| | MTX alone | | | | MTX/*cis*-Platinum | | | |
|---|---|---|---|---|---|---|---|---|
| Patient No. | Pretreatment creatinine clearance (ml/min) | $t_{½}$ ($\beta$) (hr) | AUC (hr.$\mu$mol/l) | MTX clearance (l/hr) | Pretreatment creatinine clearance (ml/min) | $t_{½}$ ($\beta$) (hr) | AUC (hr.$\mu$mol/l) | MTX clearance (l/hr) |
| 1 | 112 | 2.4 | 35.34 | 2.83 | 91 | 2.8 | 38.81 | 2.58 |
| 2(a) | 111 | 4.7 | 28.36 | 3.53 | 99 | 3.0 | 27.08 | 3.69 |
| 2(b) | 85 | 3.6 | 31.11 | 3.21 | 88 | 3.4 | 32.09 | 3.12 |
| 3 | 71 | 3.3 | 28.65 | 3.49 | 59 | 2.9 | 32.55 | 3.07 |
| 4 | 106 | 1.8 | 23.99 | 4.17 | 73 | 2.2 | 25.93 | 3.86 |
| 5 | 52 | 19.0 | 60.78 | 1.24 | 69 | 4.5 | 22.47 | 2.23 |

On day 15 prehydration was performed with 1 l of N-saline over 2 hr. The MTX 50 mg/m$^2$ was given as an intravenous bolus, followed immediately by CDDP (50 mg/m$^2$) given as a 2-hr infusion in 1 l of N-saline. Thereafter 2 further litres of N-saline were infused over 16 hr. If urine volumes fell below 100 ml/hr at any stage, 10% mannitol (100 ml) was added to the infusion over 30 min.

Blood samples after each of the above treatments were taken via an indwelling catheter at time 0, 15 min, 30 min, 45 min, 60 min, 2 hr, 6 hr, 12 hr, 24 hr and also 48 and 72 hr as required. Analysis of the serum MTX levels was performed by a rapid homogenous enzyme immunoassay method (EMIT, Syva). Folinic acid was only given if the 24-hr MTX level was greater than 0.2 $\mu$M, in which case it was continued (15 mg q.d.s. orally) until the MTX levels fell below 0.2 $\mu$M. In only one case (patient No. 5) was it necessary to continue folinic acid for longer than 24 hr.

The side-effects of this treatment were limited to the expected vomiting induced by CDDP. Haematological toxicity (WBC <2500/mm$^3$, platelets <100,000/mm$^3$) was not seen, nor was there any evidence of serial deterioration in creatinine clearance.

Responses to treatment were measured clinically and radiologically, and responding patients continued for up to 5 complete cycles of the 2-drug combination.

## RESULTS

The results are outlined in Table 1. Patient No. 2 had MTX assays performed on 2 successive complete treatment cycles of MTX/CDDP, and data from both cycles are included. For patients Nos 1–4 (with a mean pretreatment creatinine clearance of 97 ml/min) the mean $t_{½}$ ($\beta$) following MTX alone was 3.2 hr (S.D. 0.9). This is not significantly different from the mean $t_{½}$ ($\beta$) for MTX when given to the same 4 patients together with CDDP 2 weeks later (2.9 hr, S.D. 0.4). The mean values following MTX alone and following MTX with CDDP for MTX clearance were 3.54 (S.D. 0.45) and 3.26 l/hr (S.D. 0.46) respectively; these are not significantly different. Similarly, the mean areas under the curve (AUC) following MTX alone and following MTX with CDDP were 28.73 (S.D. 3.80) and 31.29 hr.$\mu$mol/l (S.D. 4.60) respectively; again, these parameters are not significantly different. These data are illustrated graphically in Fig. 1.

Patient No. 5 is considered separately because of his reduced creatinine clearance (52 ml/min) prior to therapy. As can be seen in Table 1 and Fig.

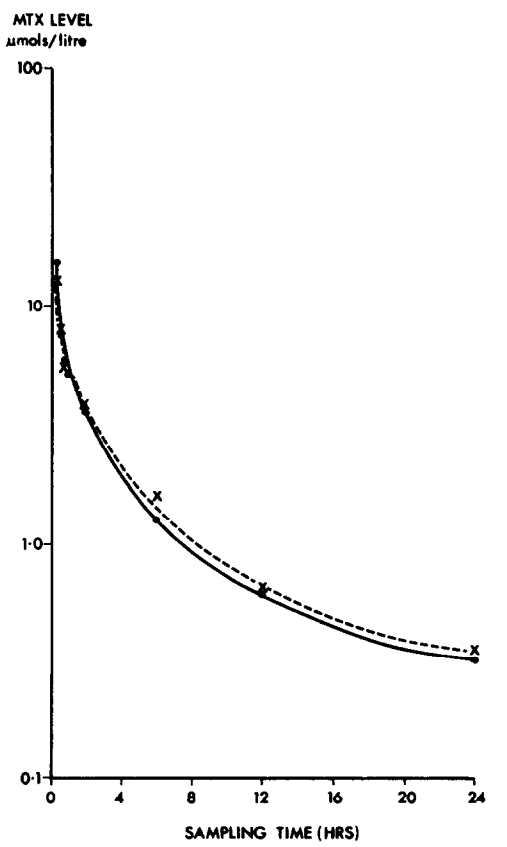


*Fig. 1. Mean MTX levels for patients Nos 1–4 when MTX was given alone (•) and when given with CDDP (×).*

2, it is apparent that the $t_{\frac{1}{2}}$ ($\beta$) for MTX was significantly longer (19.0 hr) when the drug was given alone without hydration than when given together with CDDP and a saline diuresis [$t_{\frac{1}{2}}$ ($\beta$) of 4.5 hr].

With respect to tumour response, to date 2 patients have had an objective partial response in lymph node deposits (lasting for 3+ and 8 months), while the remaining 3 patients have had stable disease for 3–9 months, including 2 patients with marked subjective reponses in bone metastases.

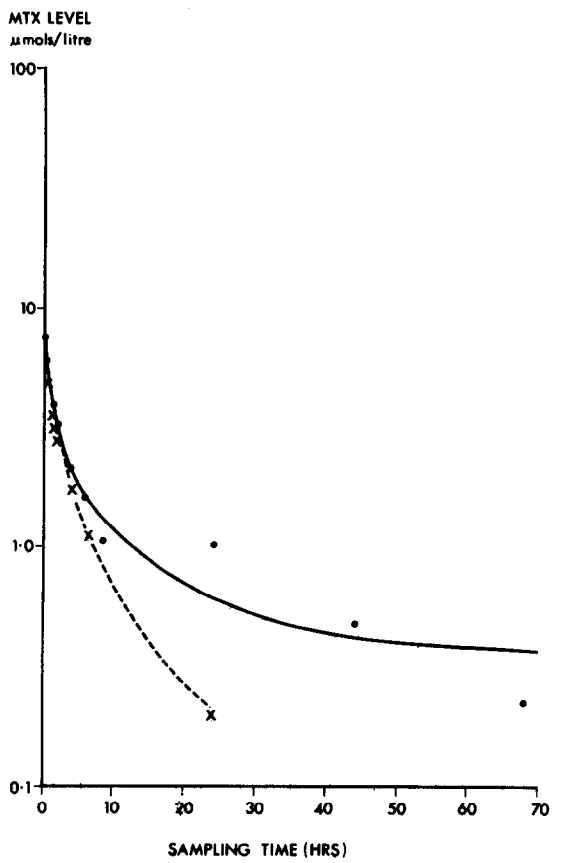


*Fig. 2. MTX levels for patients No. 5 when MTX was given alone (●) and when given with CDDP (×).*

## DISCUSSION

The potential risk of exacerbation of MTX toxicity by CDDP has led investigators using these drugs in combination for a variety of cancers to devise protocols in which the administration of the 2 drugs has been separated by some days [4, 5]. The data from this study indicate that in the presence of satisfactory renal function, MTX and CDDP may in fact be administered safely simultaneously, as long as standard methods for CDDP administration are used. Indeed, the requirement for prehydration and diuresis, which is an integral part of CDDP administration, is likely to be a positive advantage in increasing the rate at which MTX, given simultaneously, is cleared. This enhanced diuresis may have played a major part in patient No. 5's increased rate of renal clearance of MTX when it was given with CDDP. In this patient urine output immediately following MTX treatment alone was only 1000 ml in 24 hr, in comparison with urine output immediately following MTX and CDDP treatment, which was measured as 3500 ml in 24 hr.

Since MTX may be given frequently, i.e. every 1–2 weeks, because of its relative lack of myelosuppression, it is an attractive drug for inclusion in combination protocols in bladder cancer incorporating drugs such as CDDP, which would generally be given less frequently. Concurrent administration of the 2 drugs may be therapeutically important, since some experimental data have suggested a degree of synergism between MTX and CDDP, at least in animal tumours [6].

As these early data are beginning to indicate significant activity for MTX/CDDP chemotherapy in advanced bladder cancer, the lack of evidence of enhanced drug toxicity should encourage further applications for this combination in this disease.

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