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# High-Dose Methotrexate: A Clinical and Pharmacokinetic Evaluation

## Treatment of Advanced Squamous Cell Carcinoma of the Head and Neck Using a Prospective Mathematical Model and Pharmacokinetic Surveillance

R. Favre, S. Monjanel, M. Alfonsi, J. P. Pradoura, D. Bagarry-Liegey, S. Clement, A. M. Imbert, N. Lena, J. Colonna d'Istria, J. P. Cano, and Y. Carcassonne

Institut J. Paoli-I. Calmettes, 232, bd de Ste-Marguerite, B.P. 156, Marseille, Cedex 9, France

***Summary.*** *Some of 66 patients with head and neck tumors were treated with high-dose methotrexate monochemotherapy. The use of a prospective mathematical model with pharmacokinetic surveillance proved to be reliable, practical, and useful. By this means chemotherapy could be individualized, with a resultant marked reduction in the frequency and severity of toxicity. The onset of clinical toxic manifestations was significantly correlated with a poor therapeutic response and poor prognosis. The patients were classified in to three groups according to poor, intermediate, and good pharmacokinetic parameters calculated after an intravenous identification dose of methotrexate. These group allocations had a very high prognostic value with regard to toxicity, and especially to the quality of therapeutic response to high-dose methotrexate. They are suggested as useful guidelines in the prescription of high-dose methotrexate chemotherapy.*

### Introduction

Sixty-six patients with advanced squamous cell carcinoma of the head and neck received high-dose methotrexate (HD-MTX) whenever possible. Many parameters were gathered from the routine use of a prospective mathematical model with pharmacokinetic surveillance [7]. An a posteriori analysis indicates that it is nearly possible to predict both the therapeutic response and toxicity.

### Materials and Methods

*A. Patients.* The distribution of the 66 patients was comparable to that in other series, with a clear predominance of oropharynx and buccal cavity tumors (Table 1), a very high male/female ratio (64/2), and most patients 40–70 years old. The initial T staging was T3 or T4, and most patients were classed as N+. Nine patients had documented metastases, six to the bone marrow, two to the lung, and one to the liver.

The individual physiological status was grade II or III on the WHO scale or grade 6 or 7 on the Karnofsky scale.

*B. Therapeutic Protocols.* Obviously no HD-MTX was undertaken with creatininemia above 130 μmol/l [1] and/or if the usual hematologic conditions were not met.

Patients were divided into two groups. The 17 patients in group I were treated during the period when the pharmacokinetic model was being refined. Their treatment consisted of repeated HD-MTX. Each course consisted of three phases. The first corresponded to a period of 12 h for hydratation and urine alkalinization (perfusion of 3 l of 5% D/W to containing a total of 40 mEq sodium bicarbonate and 20 mEq potassium chlorure). If the urinary output and pH were adequate (output $\geqslant$ 200 ml/h and pH $\geqslant$ 7) at the end of the first phase, the second phase was begun. This consisted in a bolus injection of 50 mg MTX/m$^2$, followed by a 36-h constant-rate perfusion of 1,500 MTX/m$^2$. The third phase was folinic acid rescue. (A 25 mg/m$^2$ bolus injection was followed by a 12-h perfusion of 200 mg/m$^2$ and finally by six IM injections of 25 mg/m$^2$, each given at 6-h intervals.)

The plasma MTX levels were regularly measured, but no modifications were made to the MTX and folinic acid prescriptions.

The total doses of MTX administered and the 24-h and 36-h plasma MTX levels were analysed.

**Table 1.** Tumor localization and previous treatment[a]

| | No treatment | R | R+S | R+S+R | R+C | R+S+C | S+R | C+R | C+R+S | S+C |
|---|---|---|---|---|---|---|---|---|---|---|
| Rhinopharynx (2) | – | 1 | – | – | 1 | – | – | – | – | – |
| Oropharynx (26) | 5 | 14 | 1 | 1 | 1 | 1 | 3 | – | – | – |
| Hypopharynx + larynx (9) | 1 | 2 | 1 | – | 2 | – | 1 | 1 | – | 1 |
| Buccal cavity (26) | 3 | 8 | 1 | 4 | 2 | 1 | 2 | 4 | 1 | – |
| Other (3) | – | 1 | 1 | 1 | – | – | – | – | – | – |
| Total (66) | 9 | 26 | 4 | 6 | 6 | 2 | 6 | 5 | 1 | 1 |

[a] R, radiotherapy; S, surgery; C, chemotherapy

*Send offprint requests to* Dr. Roger Favre

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**Table 2.** Therapeutic responses and toxicities

| | Response not assessed | Poor response | | Good response | | MTX IV only |
|---|---|---|---|---|---|---|
| | Group I | Group I | Group II | Group I | Group II | Group II |
| Rhinopharynx (2) | 1[a] | 1[a] | – | – | – | – |
| Oropharynx (26) | 1[a] | – | 13[a, a, a, a, b] | 3 | 3 | 6[a] |
| Hypopharynx + larynx (9) | – | 2 | 2 | – | 3 | 2 |
| Buccal cavity (26) | 1 | 6[b, b] | 5[a] | 1 | 6 | 7[a] |
| Other (3) | – | 1 | 1 | – | 1 | – |
| Total (66) | 3 | 10 | 21 | 4 | 13 | 15 |

[a] Mucosal toxicity
[b] Oliguria

The second group included 49 patients treated after the pharmacokinetic model was established. Their management differed, since they all received an IV identification dose of MTX (MTX-IV-ID), which permitted calculation of their individual pharmacokinetic parameters for MTX, clearance (Cl), and terminal half-life time ($t_{1/2}$). It was possible to calculate the individual doses of MTX that, given at a constant rate over a 36-h perfusion, would permit to achievement of a steady plasma concentration of MTX ($10^{-5}$ *M*/l).

The mathematical model is simple: $Q = P \times Cl \times T$; where Q is MTX dose, P is the steady plasma concentration, Cl is the clearance, and T the duration of infusion.

The MTX-IV-ID was administered after the usual 12-h period for hydratation and urine alkalinization. Each patient received an IV bolus of 50 mg MTX/m$^2$ and blood samples were subsequently collected at 0, 15, and 30 min and at 1, 3, 6, 12, 24, and 30 h. No folinic acid rescue phase followed.

The HD-MTX courses themselves began at least 1 week after the MTX-IV-ID and were repeated 3 weeks apart thereafter. As for the first group, the HD-MTX treatment was divided into three phases. The first phase is the same. The second phase consisted in the 36-h perfusion of MTX at a constant rate. The desired plateau level of MTX ($10^{-5}$ *M*/l) was achieved 6–8 h after the beginning of the perfusion [7]. Two blood samples were collected, at 6 and 24 h. They were used to adjust the ongoing MTX perfusion if necessary to keep more closely to the desired level.

In the third phase, the patients were given perfusions of 500 ml 5% D/W containing 100 mg folinic acid/m$^3$ over 6 h. This perfusion was repeated as long as the plasma MTX level was below $10^{-7}$ *M*/l. Blood samples were collected 36, 49, and 54 h after the beginning of the HD-MTX perfusion.

The parameters analysed are the total doses of MTX in each course, the 24-h and 36-h plasma levels during HD-MTX perfusion, the duration of folinic acid rescue and, finally, the residual plasma level.

Two methods were used for measurement of plasma MTX concentration. A radioisotopic method [8] with good sensitivity ($2.5 \times 10^{-9}$ *M*) was used after the MTX-IV-ID. The second method was enzymatic; it is rapid and therefore useful in dosage adjustment during the MTX perfusion or in the adjustment of the duration of folinic acid rescue [2]. The two methods were used for all tests, a slight underestimation being established with the enzymatic method. The $t_{1/2}$ was calculated from the data of the MTX-IV-ID after 12 h of excretion.

The therapeutic responses were divided into four categories [11]: first, the therapeutic response could not be assessed; second, there was no response at all or tumor regression less than 50% (NR); third, tumor regression by more than 50%, which was classed as a partial response (PR); and finally, a complete response (CR). Patients with partial and complete responses (PR + CR) were designated good responders, while patients with no response or tumor regression by less than 50% were designated poor responders.

*C. Statistical Analysis.* All results were analysed for significance by the R. A. Fisher cumulated distribution [4] method or [10] by the Chi-square test. $P < 0.05$ was assessed as significant (S) and $P < 0.01$ as highly significant (HS).

## Results

### *A. Clinical Data*

Patients with oropharyngeal tumors (Table 2) were less responsive than others ($P < 0.05$).

Clinical toxicities observed were mucositis or renal impairment; there was no aplasia or hepatic toxicity. The toxic effects were only observed in poor responders ($P < 0.001$), but there was no correlation between toxicity and performance status. In group II toxic effects were less pronounced, and they were also more frequent in patients with oropharyngeal tumors ($P < 0.05$).

Fifteen patients received only a MTX-IV-ID. Even with a relatively low dose (50 mg/m$^2$) two major mucosal toxicities were observed. For eight of the patients, inadequate urinary pH or output during hydratation and alkalinization of the first trial of HD MTX perfusion contraindicated continuation of the course of treatment. In the other seven cases general contraindications caused treatment with HD MTX to be abandoned even before the date planned for the first perfusion.

HD MTX could be given for a longer period (Table 3) and with a better survival in good responders ($P < 0.01$).

**Table 3.** Overall results in 48[a] patients with evaluable response receiving one or more courses of HD-MTX

| | No. of patients | No. of courses of HD-MTX | Survival (months) | |
|---|---|---|---|---|
| | | | Mean | Median |
| Poor response (NR) | 31/48 (64.6%) | 1.9 ± 1.3 | 2.3 ± 2.3 | 2 |
| Good response (PR) | 17/48 (35.4%) | 4.2 ± 2.3 | 8.8 ± 9.3 | 7 |

[a] Group I contained 14 patients and group II, 34

**Table 4.** Mean MTX perfusion parameters of group I patients

| | MTX dose (mg) | Plasma MTX levels ($10^{-8}$ *M*/l) | |
|---|---|---|---|
| | | 24th h | 36th h |
| Response not assessed | 2,417 ± 520 | 1,188 ± 611 | 791 ± 623 |
| Poor response (NR) | 2,369 ± 389 | 2,059 ± 1,588 | 1,431 ± 737 |
| Good response (PR) | 2,250 ± 654 | 1,487 ± 1,524 | 457 ± 182 |
| Significance (NR/PR) | NS | NS | S |

There was no correlation between the therapeutic response and previous treatment with MTX, the time since previous treatment and HD-MTX, or performance status.

None of the nine patients with documented distant metastases was a good responder.

Substitution polychemotherapy was not effective in patients who only had MTX-IV-ID or in poor responders, and was only occasionally effective in good responders.

The overall survival in the 66 patients from the time of the MTX-IV-ID was 4.4 ± 5.2 months, the median being 2.5 months.

### *B. Pharmacokinetic Data*

*a) Group I.* The mean dose of MTX given in each course was 2,355 ± 435 mg (1,500–3,000 mg). Whatever the dose perfused, wide variations were observed in plasma levels from one patient to the other, and even in the same patient during different courses of treatment.

The 36-h plasma MTX level (Table 4) was significantly lower ($P < 0.05$) in good responders, corresponding to more rapid excretion.

*b) Group II.* The variations in the observed plasma MTX levels were less pronounced than in the first group. The theoretical desired plasma levels were very satisfactorily achieved, and the method proved easy to apply. There was a significant difference between pharmacokinetic parameters and therapeutic responses or toxicities (Table 5).

Once more, good responders excreted MTX faster than others, and in patients with clinical intolerance MTX excretion was clearly slower.

**Table 6.** Pharmacokinetic parameters of group II patients who only had MTX IV-ID and those who received HD-MTX without toxicity

| | Mean Cl (l/h) | Mean $t_{1/2}$ (h) |
|---|---|---|
| Patients receiving MTX IV-ID only (15) | 7.8 ± 4.1 | 7.5 ± 2.8 |
| Patients receiving HD-MTX without toxicity (28) | 10.5 ± 4.3 | 5.8 ± 2.0 |
| Significance | S | S |

The pharmacokinetic parameters of the group of 15 patients who only received the MTX-IV-ID were poor, comparable to those of patients presenting clinical toxicity after HD-MTX but different from those of patients without toxicity (Table 6).

*c) Predictive Value of the Pharmacokinetic Parameters, After the MTX-IV-ID.* The numerous differences observed between the patients in Cl and $t_{1/2}$ led to an a posteriori subdivision of the patients into three categories. Patients in the first category had poor parameters with Cl ≤ 6 l/h or $t_{1/2} \geq 8$ h; those in the second category had intermediate parameters, with Cl between 6 and 9 l/h and $t_{1/2} < 8$ h; and patients in the third category had good parameters, with Cl > 9 l/h and $t_{1/2} < 8$ h.

The percentage of good responders in categories 1, 2, and 3 were, respectively, 0%, 50%, and 60% (Table 7). Of 21 poor

**Table 7.** Pharmacokinetic parameters following MTX IV-ID and therapeutic response to HD-MTX in group II patients

| | $t_{1/2} \geq 8$ h or Cl ≤ 6 l/h | $t_{1/2} < 8$ h and | | Total |
|---|---|---|---|---|
| | | 6 l/h < Cl ≤ 9 l/h | Cl > 9 l/h | |
| Poor response (NR) | 11 | 4 | 6 (10) | 21 |
| Good response (PR) | 0 | 4 | 9 (13) | 13 |
| Total | 11 | 8 | 15 (23) | 34 |

**Table 5.** Mean pharmacokinetic parameters of group II patients (34) who received one or more courses of HD-MTX

| | MTX IV-ID | | HD-MTX Perfusion ($10^{-8}$ *M*/l) | | | | | Folinic acid rescue (h) |
|---|---|---|---|---|---|---|---|---|
| | Cl (l/h) | $t_{1/2}$ (h) | Cl (l/h) | MTX dose (mg) | MTX plasma level ($10^{-8}$ *M*/l) | | | |
| | | | | | 24th h | 36th h | Residual | |
| Poor response (NR) | 9.8 ± 4.0 | 7.2 ± 2.9 | 8.5 ± 3.2 | 1,401 ± 364 | 1,133 ± 772 | 955 ± 319 | 17.4 ± 10.5 | 30.5 ± 9.8 |
| Good response (PR) | 11.3 ± 4.3 | 5.2 ± 1.0 | 10.5 ± 3.0 | 1,744 ± 400 | 1,097 ± 218 | 972 ± 343 | 10.1 ± 4.2 | 31.6 ± 5.1 |
| Significance | NS | S | S | S | NS | NS | S | NS |
| Toxicity (6 patients) | 9.6 ± 3.0 | 10.4 ± 4.8 | 7.0 ± 2.7 | 1,358 ± 369 | 1,638 ± 1,290 | 839 ± 295 | 23.6 ± 12.4 | 38.9 ± 2.6 |
| No toxicity (28 patients) | 10.5 ± 4.3 | 5.8 ± 2.0 | 9.8 ± 3.2 | 1,552 ± 472 | 1,020 ± 277 | 1,024 ± 275 | 13.3 ± 7.6 | 26.5 ± 11.5 |
| Significance | NS | H.S. | S | NS | S | NS | S | S |

**Table 8.** Terminal half-life time and toxicity in group II patients receiving HD-MTX

| | $t_{1/2} \geq 8$ h | $t_{1/2} < 8$ h | Total |
|---|---|---|---|
| Toxicity | 5 | 1 | 6 |
| No toxicity | 3 | 25 | 28 |
| Total | 8 | 26 | 34 |

**Table 9.** Group II patients receiving MTX IV-ID only: pharmacokinetic parameters and contraindications to HD-MTX

| | $t_{1/2} \geq 8$ h or Cl $\leq$ 6 l/h | $t_{1/2} < 8$ h and | | Total |
|---|---|---|---|---|
| | | 6 l/h < Cl $\leq$ 9 l/h | Cl > 9 l/h | |
| Inadequate urinary pH or output | 4 | 2 | 2 | 8 |
| General contraindications | 6 | 1 | 0 | 7 |
| Total | 10 | 3 | 2 | 15 |

responders, 11 had poor pharmacokinetic parameters while 13 of 13 good responders had intermediate or good parameters ($P < 0.01$). The prognostic value of the pharmacokinetic parameters was 70.6%, with virtual certainty that poor parameters are followed by a poor response.

In the second category (intermediate parameters), it was observed that the clearance of four good responders, as calculated from the first HD-MTX course, was over 9 l/h, while it was lower than 9 l/h in the four poor responders.

The MTX clearance was of no value in the prediction of clinical toxicities, but five of eight patients with $t_{1/2} > 8$ h (Table 8) were affected by a clinical toxicity ($P < 0.001$). The individual $t_{1/2}$ values were of predictive value in 30 of 34 patients, or more than 90%.

Only two of 15 patients who only received MTX-IV-ID had good parameters (Table 9).

## Discussion

The results demonstrated that HD-MTX perfusion was practicable and that the prospective mathematical model utilized with pharmacokinetic surveillance was good.

The observed 35% good therapeutic response closely reflected reality. Survival remains short even in good responders, with a mean of 8.8 months and a median of 7 months. The overall survival was also poor, with a mean of 4 months and a median of 2.5 months. The way this HD-MTX therapy was executed is only a first step in the rationalization of this type of chemotherapy.

One could wonder whether the previously untreated patients might not artificially increase the percentage of good responders. In fact, if these patients are excluded this percentage is not modified. We also considered whether the good responders were not simply patients who were able to tolerate higher total doses of MTX. Such an hypothesis could not be radically discarded, but even though the difference was not significant, at least for the first group the MTX doses received by good responders were lower than those received by poor responders.

There is a significant difference in reactivity to other chemotherapy between good and poor responders. This difference could not be attributed to previous treatments, since many good responders had already received successive chemotherapies, or to other general causes such as performance status.

Good responders had better excretion of MTX, but this was expressed differently in the two groups. In group I, where the dose was fixed according to body surface area, the plasma MTX levels were low at the end of the perfusion. In the second group, where a constant plasma level was maintained according to the indications of the pharmacokinetic parameters, significantly higher doses of MTX were given in each course to good responders. This indicated better excretion of MTX, as illustrated by significantly lower post-perfusion plasma levels of MTX. Perhaps a qualitative difference in MTX metabolism might cause apparently better excretion. More knowledge about MTX metabolism and the fate of its different metabolites (7-OH-MTX, DAMPA, and polyglutamates, etc.) could be useful in providing answers to many unresolved problems [6, 9].

There was no positive correlation between toxicity and a good therapeutic response, as one might have imagined. On the contrary, it could be proposed that HD-MTX is contraindicated in those patients manifesting toxicity after the first therapy, especially if they have an oropharyngeal tumor.

The toxicities were much more severe and frequent in group I (30%) than in group II (17.5%).

The outlook with HD-MTX treatment is better in group II (some patients did not receive HD-MTX because their urinary output and/or pH was inadequate or their pharmacokinetic data were unfavorable); the modulations achieved with folinic acid and rescue are also more hopeful.

Generally, patients in group I received higher doses of MTX than those in group II (2,355 ± 435 mg and 1,535 ± 409 mg, respectively).

The patients affected by toxicity had received 2,225 ± 635 mg and 1,358 ± 369 mg in groups I and II, respectively, both doses being lower than the mean dose given in each group.

Toxicities in the patients in group II were clearly related to slow MTX excretion [3, 5, 12]. Their residual plasma level was significantly higher, and folinic acid rescue lasted significantly longer. One could argue that folinic acid rescue and alkalinization were not sufficiently prolonged.

Many patients who would ultimately be poor responders or at greater risk of toxicity are identified with the MTX-IV-ID. It is useless to treat patients in the first category, while HD-MTX is indicated in third category. For the second category, the results of the first course of HD MTX should be carefully considered before a decision on further treatment is reached.

In the light of this present study, it is interesting to look at what might have happened if the patients had first been categorized according to their pharmacokinetic parameters, as calculated from the MTX-IV-ID data. Of 49 candidates (group II) to HD-MTX, 15 would have been discarded right away, whatever pharmacokinetic parameters were recorded. Of the 34 other patients who received at least one course of HD-MTX, only 23 would have received repeated cures, 13 of whom were in fact good responders (57%).

If the individual MTX Cl and $t_{1/2}$ are considered patients can be spared useless alkalinization/hydratation periods and even more useless chemotherapy and toxicity.

## Conclusion

The present study demonstrated that HD-MTX with the use of a prospective mathematical model and pharmacokinetic surveillance was practically possible in any structured cancer unit. In the treatment of advanced squamous cell carcinoma of the head and neck, this quite sophisticated method contributed to a clear reduction in both frequency and severity of toxic side-effects.

The observance of clinical toxic effects in any patient was correlated with a bad therapeutic response, mostly in patients with oropharyngeal tumors. There was a good correlation between desired and observed plasma levels of MTX.

A good therapeutic response was coupled with rapid excretion of MTX. The clearance and half-life calculated following the MTX-IV-ID permitted preliminary division of the patients into three categories, which proved to be a good guide as to whether HD-MTX therapy was indicated and whether toxicity was probable.

Advising against HD-MTX for patients with unfavorable parameters and recommending it for patients with intermediate and good parameters can avoid useless and costly chemotherapies in more than one patient out of three and abolish any risk of toxicity.

This should allow an increase in the present 35% rate of good responses.

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