An Open Label Phase I Pilot study of Continuous Intra pleural Infusion of Escalated Doses of Methotrexate in Malignant Pleural Mesothelioma

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OBJECTIVE

Malignant pleural mesothelioma is an aggressive disease that is deadly & difficult to treat with a median overall survival of about one year.[1] Systemic high dose methotrexate yielded highest responses but systemic toxicity has been dose limiting.[2] The current study aimed to evaluate the toxicity from escalated methotrexate doses infused intra-pleural over five days and to determine the pleural and systemic drug levels with this chemotherapeutic modality.

PATIENTS & METHODS

Five patients with malignant pleural mesothelioma were treated with three cycles of intra pleural methotrexate infused through a pig tail catheter inserted in the pleural space. Methotrexate levels were estimated in the pleural fluid and serum once daily throughout the treatment cycles. Fourteen days between cycles were calculated from the last day of the previous cycle. The total dose for each cycle was infused over five days with simultaneous intravenous calcium folinate. The total cycle dose for the first, second and third cycles were; 300mg/m^2, 501 mg/m^2 and 750.5 mg/m^2 respectively. Patients were excluded if developed any grade II toxicity according to Common Toxicity Criteria (CTC) version IV grading system[3]

RESULTS

The mean serum methotrexate level was 1.72 µmole/l while that of the pleural fluid was 503.224 µmole/l. The mean serum/ pleural ratio was 0.00396, while the pleural/ serum ratio was 396.21.

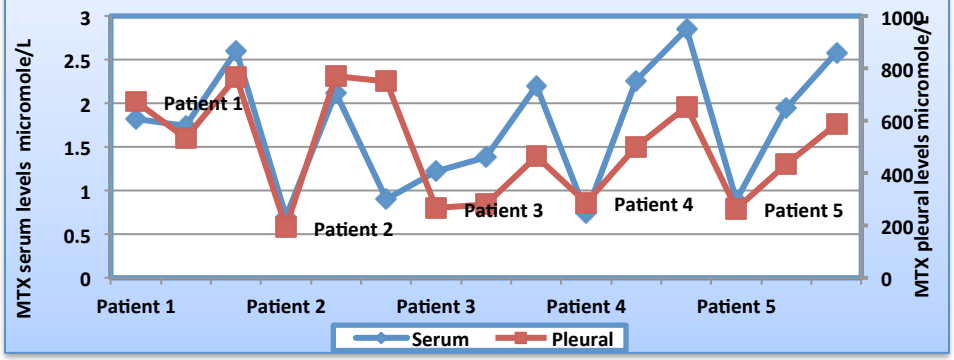
No remarkable toxicity was observed in the 5 patients except for; patient 1 who developed fluid leakage around the puncture site. Patient 2 developed grade I hepatotoxicity and both patients developed grade I pleuritic chest pain and dry irritative cough.

Table 1. Pleural & serum levels in individual patients over the 3 cycles

Levels	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Pleural levels					
Cycle 1	674.46 ±122.40 (n=5)	192.35 ± 114.7 (n=5)	265.8 ± 152.91 (n=5)	286.8 ± 60.15 (n=5)	264.8 ± 60.93 (n=5)
Cycle 2	660.64 ±118.62 (n=5)	770.148 ± 95.84 (n=5)	280 ± 201.45 (n=5)	500.6 ± 30.15 (n=5)	433.6 ± 91.95 (n=5)
Cycle 3	765.76 ±181.73 (n=5)	751.6 ± 399.07 (n=5)	462.4 ±173.95 (n=5)	653 ± 130.52 (n=5)	586.4 ± 82.99 (n=5)
Serum levels					
Cycle 1	1.82 ± 0.48 (n=5)	0.7± 0.167 (n=5)	1.216 ± 0.789 (n=5)	0.736 ± 0.37 (n=5)	0.89 ± 0.419 (n=5)
Cycle 2	1.74 ± 0.476 (n=5)	2.12 ± 1.42 (n=5)	1.38 ± 0.629 (n=5)	2.26 ± 0.434 (n=5)	1.94 ± 0.477 (n=5)
Cycle 3	2.6 ± 1.25 (n=5)	0.9 ± 0.71 (n=5)	2.2 ± 0.69 (n=5)	2.85± 0.376 (n=5)	2.58 ± 0.433 (n=5)

Values are represented as mean ± S.D. Serum & pleural methotrexate levels are in µmole/l.

Figure1. Mean Methotrexate serum versus pleural levels for each patient over 3 cycles



REFRENCES:1-Tsao AS, Wistuba I, Roth JA, et al. Malignant pleural mesothelioma .*J Clin Oncol*. 2009;27: 2081-2090.

2-Solheim OP, Saeter G, Finnanger AM, et al. High dose methotrexate in treatment of malignant mesothelioma of the pleura: A phase II study. *Br. J. Cancer.* 1992;65: 956-960.

3-Common Terminology Criteria for Adverse Events (CTCAE)-PDQ (Database online). Version 4.0 *National Cancer Institute.* 2010;V4.03: June 14.

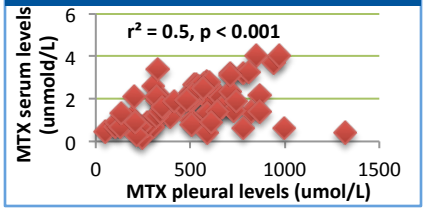
CONCLUSION

This study demonstrates no grade II toxicity from 750.5mg/m^2 of methotrexate infused intra pleural over five days. This approach allows attaining methotrexate pleural levels that are 95- 3000 times higher than systemic serum levels, with minimal toxicity

Table 2. Descriptive statistics of serum & pleural samples in all patients over the 3 cycles

Parameters	Mean ± S.D	Range
Serum levels (n=75)	1.73 ± 0.94	0.15- 4
Pleural levels (n= 75)	503.2 ± 246.76	51.46 - 1319
Serum/pleural ratio	0.00396 ± 0.002	0.0003 - 0.01
Serum/ pleural %	0.387 ± 0.22	0.03 – 1.04
Pleural/serum ratio	396.219 ± 438.45	95.7 - 3067.4

Figure 2. Correlation between Methotrexate pleural & serum levels



RECOMMENDATIONS

The current results mandate performing a randomized controlled trial to assess modality efficacy & applicability.