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Do periprosthetic seromas contribute to a third space effect after high dose Methotrexate?

Claudia Heu¹, Volker Strenger¹, Joanna Szkandera¹, Joerg Friesenbichler¹, Georg Prattes¹, Ernst-Christian Urban¹, Andreas Leithner¹

¹ Medical University of Graz, Austria

BACKGROUND Beside surgery, high dose Methotrexate is a mainstay of osteosarcoma treatment. However, it is associated with severe side effects, which partly are dose dependent. Methotrexate tends to accumulate in tissues and cavities (third spaces) leading to local toxicity and delayed elimination. In order to avoid this, considerable periprosthetic seromas are punctured in our institution, despite an increased risk of infections. The aim of our study was to analyse Methotrexate concentrations in seroma and blood to verify a potential toxic risk based on a third space effect.

METHODS In a monocentric data analysis of 53 consecutive osteosarcoma patients (5 – 46, median 15 years) who had received an endoprosthesis and who were treated with high dose Methotrexate from 1991 till 2011, we retrospectively compared Methotrexate concentrations in seromas with the corresponding (+/- 8 hours) concentrations in blood.

RESULTS 114 periprosthetic seroma punctures were performed in 18 of 53 patients (median 5 punctures per patient, range 1 - 20 punctures per patient). The amount of punctured effusions was documented in 101 punctures, ranging from 5 - 420 ml (median 150 ml). Methotrexate concentrations were determined in 61.1% of all punctures and were 249 – 4397% (median 1586%) of the corresponding blood concentration at 24 hours. 48 and 72 hours Methotrexate concentrations of seromas were 236 – 535% (median 950%) and 166 – 682% (median 366%) of the corresponding blood concentrations, respectively. Especially the 24 hours measurements of the seromas ranged up to highly toxic concentrations of 170.74 µmol/l (median 109.83 µmol/l, range 4.91 - 170.71 µmol/l) in comparison to a median value of 4.65 µmol/l in blood (range 0.68 - 44.38 µmol/l, p=0.001 (Wilcoxon test)). Similar statistically significant differences indicating a third space effect were observed at 48 (p<0.001) and 72 hours (p=0.015).

CONCLUSIONS In conclusion, Methotrexate concentrations of effusions are significantly higher than corresponding blood levels indicating that periprosthetic seromas might act as a third space after high dose Methotrexate, potentially leading to severe local and systemic side effects. These effusions should therefore be punctured in order to avoid increased toxicity.

E-mail (main author): claudia.heu@stud.medunigraz.at