www.nicoledelepine.fr

FEASIBILITY OF VERY HIGH DOSE METHOTREXATE (VHD MTX) 12G/M² TO 34 G/M²: A RETROSPECTIVE STUDY OF 771 COURSES PERFORMED IN 46 PATIENTS WITH HIGH RISK OSTEOSARCOMA (OS)

Introduction:

Since the 1975, Jaffe and Rosen's protocols, MTX is considered as the major drug in OS treatment. The prognostic significance of MTX dose intensity and serum peak on outcome of our patients with OS led us to propose increased doses of MTX with increased doses of Leucovorin rescue in patients with poor prognostic OS. The aim of this study is to analyze feasibility and long term toxicity of very high doses.

Patients and methods:

From July 1986 to December 1995, we performed 771 courses of Very High Doses MTX (VHD MTX) in 46 patients (18 girls, 28 boys-4 to 23 years. The indications of VHD MTX were high risk OS (metastases at diagnosis, recurrences after conventional treatment (local or metastasis) , unfavourable histology like chondroblastic osteosarcoma). 12g /m² to 34 g/m² were infused per course in a 6 hours IV infusion. The initial dose of MTX depended of age, the initial dose of leucovorin rescue depended of MTX dose. We performed MTX pharmacokinetics for efficacy (serum peak at H6), for toxicity (H24, H48, H72, etc), regular clinical and biological bloods exams. Side effects were treated by increased dose of Leucovorin rescue, IV alkaline infusion and supportive haematological or renal care. To avoid cross toxicity, no other medicine was given during the MTX course.

Results:

The most frequent toxicity was hepatic (70 % patients, 19% courses, 5 acute toxicities, followed in order by haematological and renal toxicity. These toxicities increased in frequency and severity with doses of MTX. We although observed neurological and cutaneous toxicity, not dose- depending. All toxicities were most often associated with delayed elimination of MTX. No toxic death occurred. Hepatic toxicity is the limiting factor to increase MTX dose. Delayed elimination was not often associated with severe side-effects. Toxicity leaded us to decrease the following dose and /or delayed the following course or stop MTX.

As usual with conventional high dose MTX , no late toxicity was observed

Conclusion:

In the literature, it‘s difficult to find teams which give more than 12g/sqm MTX for osteosarcoma. In our experience, very high dose MTX is feasible without toxic death if prevention and treatment of toxicity are managed by an experimented team. Efficacy and indications of very high doses methotrexate need further studies.