LONG TERM RESULTS OF OSDD PROTOCOL WITH TAILORED DOSE OF METHOTREXATE FOR NON METASTATIC HIGH GRADE OSTEOSARCOMA

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Introduction : Since the publications of Jaffe (1, 2) twenty five years ago, numerous studies have shown the central importance of High Dose Methotrexate (HDMTX) on primary or metastatic osteosarcoma in combination chemotherapy. However, the optimal dose of Methotrexate (MTX) remains controversial and the prognosis of bad responders to preoperative chemotherapy remains poor. This non randomised study addresses the effects on the primary tumor of preoperative HDMTX administered as a single preoperative agent and the influence of escalating dosage with pharmacologic monitoring, on dose, toxicity, response and survival.

Material and methods **:** *Inclusion criteria :* From November 1985 through November 2000, 46 patients aged 30 or less with primary high grade osteogenic sarcoma or MFIL fulfilled the inclusion criteria of this study : non metastatic, resectable tumor, previously untreated, definitive local treatment administered by the surgeon of the team, after short preoperative chemotherapy based on HDMTX with individualised doses administrated in public hospital.
Patients : 29 men and 17 women with a median age of 16.6 (age rage 7 to 30 years) were studied. 3 patients had upper limb lesions (2 humerus and 1 scapula), 43 lower limb locations (28 femoral, 11 tibial, 2 fibulas and 2 innominate bones). The median largest diameter of tumor was 10.5 centimeters (5-28). 2 patients had skip metastases on the same bone (2 femur, 1 tibia). *Treatment scheme (figures 1 and 2 DD1 and DD11 protocols) :* All patients were treated by a multidrug regimen derived from Rosen's T10 protocol with some differences in dose of MTX, pharmacokinetics monitoring and adjunction of Ifosfamide. They received escalating doses of MTX with clinical and pharmacokinetic monitoring. The dose of the first course was adapted to age, first course 5-9 years : 18g/m², 10/15 years : 15 g/m², > 15 years : 12 g/m², the doses of subsequent courses were adapted to the serum pharmacokinetics of each patient and to the response of the tumor in order to reach a serum peak of 1000 µmol/l at the end of the 6 hours infusion and to achieve an objective clinical response. MTX dose was escalated with an increment of 2 gr/sqm to 4 gr/sqm if the serum peak was under 1000 µmol/l or if persistent pain, swelling, local hyperthermia or alkaline phosphatases raised concern about possible ineffectiveness of the chemotherapy. *Local treatment* : All patients were operated by the same surgeon and all underwent limb salvage as primary treatment. Surgical treatment was completed with adjuvant local radiotherapy in eight cases of marginal resection in bad responders.

Results **:** *Pharmacokinetics* : In our cases, the pharmacokinetics of MTX were bicompartmental in 95 % of cases. The maximum serum peak (H6) is highly correlated with the area under the curve and represents a good evidence of he therapeutic intensity. The serum peak increases with the dose of methotrexate per square meter. Correlation between H6 (in µmol/l) and dose (in gr/sqm) in linear but with a very large interindividual variability, the mean standard deviation equals half of mean value. *Influence of clinical and pharmacokinetics monitoring on given dose and toxicity :* Dose escalation was necessary in 80 % of cases (37/46) due to low serum peak (13), or lack of clinical response (9) or both (15). The average dose increase was 40 % of the first given dose. All together, during the preoperative phase our patients received a mean dose of 14.3 gr/m²/course (min. 8 g/m², max 24 g/m²), resulting in a mean H6 serum concentration of 1248 µmol/l (570-3600). This large dose escalation did not increase dramatically the overall toxicity because, in most cases, dose escalation was made in fast excreters with initially too low serum peaks and benefited from reinforced leucovorin rescue.
Toxicity : Gastro-intestinal toxicity was observed in 3 patients (6 %) and increasing of transaminases (x 3) in 10 (20 %). Neurotoxicity appeared in 7 patients (15 %) after the second or the third course of HDMTX. No delay in chemotherapy was necessary during the preoperative phase. *Postoperative chemotherapy : The hematologic toxicity* was the most frequent toxicity ; who grade 4 in 90 % of IPA. The hepatic toxicity was the main limiting factor of postoperative MTX dose intensity. Predisposing factors were prior virus hepatitis. All together elevated transaminases and/or LDH and/or alkaline phosphatases were observed in 15 patients (30 %), and low TP in 10 (5 patients). This hepatic toxicity

resulted in delay of chemotherapy for 60 courses of MTX (7 %) and in early stopping of MTX for 4 patients. *Response to preoperative chemotherapy :* The histological response to chemotherapy was graded good in 25 and bad in 21. All together, patient received an average of 250 g/sqm MTX in 41 weeks resulting in a mean MTX intensity of 6.3 g/m²/week and a mean value of serum peak of 1380 µmol/l. 1 local recurrence was observed in a patient after early stopping of MTX and relative MTX intensity < 33 % of the planned dose. All 46 patients were initially treated by en bloc resection with limb salvage. The median size of resection was 15 centimeters. With a median follow up of 10 years, 35 patients were reoperated, for lengthening of prosthesis (9 cases), loosening (11), infection (10), or polyethylene wear (6). 4 patients were amputated : 1 for local recurrence and 3 for recurrent infection. At last consultation, the functional result, EMSOS rating was excellent in 21, good in 17, fair in 4 and poor in 4. *Final outcome*. In the 46 patients, we observed one local recurrence and 7 distant relapses (4 lung metastases and 3 primary bone). The average time to relapse was 25 months (8-75). 2 patients died of disease. 2 patients are living with evolutive disease. All others are in complete remission. The actuarial 10 year DFS in 91 %. The EFS 81 % and the OS : 94 %.

Conclusion : In our patients, clinical evaluation of the primary and pharmacokinetics monitoring permits : 1. The dose of methotrexate given, the dose intensity and the serum concentration X time of MTX, to be increased by 40 % in patients who needed it. 2. The event free, the disease free and the overall survival rate of patients to be increased. 3. Without severe increase of toxicity.
Such an individualised treatment is feasable and should be considered for every patient with localised osteosarcoma. In 2001, treatment protocols for high grade osteosarcoma should no longer require not only a good total (> 240 g/sqm) dose of MTX but a serum peak (or area under the curve) over 1000 µmol/l after 6 hours infusion or 1450 µmol/l after 4 hours infusion.