Long-term results of comprehensive treatment for non-metastatic primary limb high-grade osteosarcoma (O.S.). Emphasis of escalating high dose methotrexate (HDMTX)

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Purpose of this study

Evaluation of effects of escalating induction HDMTX on toxicity, response of tumours and survival of patients with osteosarcoma

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Patients

From 1/85 to 12/2000:
46 patients with non metastatic limb osteosarcoma, previously untreated.
29 M, 17 F
(7 - 30 y, mean : 16.6)
were treated in one of AP-HP oncologic service

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Size of the tumours

Median largest diameter was 10.5 centimeters (5-28).

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MTX dose of first course was adapted to age
5-9 y : 18 g/m²,
10/15 y : 15 g/m²,
> 15 : 12 g/sqm.
For the same dose
inter patient variability of
serum peaks was high.

SERUM PEAKS OBSERVED AFTER 12 G/M² (6 hour infusion)

inter patient variability of serum peaks with 12g/sqm

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MTX was escalated from 2 to 4 gr/sqm if
- the serum peak H6 < 1000 µmol/l
- or in case of clinical ineffectiveness.
Correlation between H6 and dose

In each patient, the correlation between H6 (µmol/l) and dose (gr/sqm) was linear.

**Pharmacokinetics**: In our cases, the pharmacokinetics of MTX were bicompartamental in 95% of cases. The maximum serum peak (H6) is highly correlated with the area under the curve and represents a good evidence of the therapeutic intensity.

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Escalation was necessary in 80% of patients (37/46) due to
- low H6 (13),
- lack of clinical response (9)
- or both (15).

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Preoperative dose escalation

Average increase of dose was 40 % p. received a mean preoperative dose : 14.3 gr/m²/course (8-24 g/m²),

mean H6 : 1248 µmol/l (570-3600).
Observed toxicity

- Induction therapy was well tolerated.
- The most frequent postoperative toxicity was hematologic grade 4:
  90% of IPA (IFO, CDDP, ADR).
Limiting factor of dose escalation

Hepatic toxicity was the main limiting factor of postoperative MTX.

Observed in 60 courses of MTX (7%) it resulted in early stopping of MTX in 4 patients.
radiological responses

- Good in 30
- Stable disease: 12
- Inevaluable: 4

Bone healing of fracture

After 4 curses

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Local treatment

All patients were primarily treated by limb salvage even in case of:

- Huge tumor
- Young child
- Fracture

- Young child
- Periacetabular resection+prosthesis
- Fractured sarcoma

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Histological Response

Graded according Huvos and Rosen criteria was:
- **good**: in 25,
- **bad**: 21.
Total doses of MTX therapy

- given dose of MTX Averaged 250 g/sqm in 41 wks.
- Mean MTX intensity 6.3 g/m²/week,
- Mean value H6 : 1380 µmol/l.
Oncologic results

- **Relapses**: out of 46 patients, we observed **one local and 7 distant relapses**
  - 4 lung, 3 bone.
  - Average time to relapse was 25 m. (8-75).

- **Final outcome**:
  - 2 p. died, 2 p. are living with evolutive disease
  - 42 others are in CR
Oncologic results

- Actuarial 10 year OS is 94%.
- 10 y DFS: 91%.
- 10 y EFS: 81%.

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Conclusion 1

- In our patients escalating doses following Rosen’s rules and pharmacokinetics monitoring permits:
  - 1. The given dose of methotrexate, the dose intensity and the serum concentration \( X \) time, to be increased by 40% in patients who needed it.
  - 2. To increase the event free, the disease free and the overall survival rate of patients.
  - 3. Without severe increase of toxicity
Conclusion 2

- Protocols for OS should require not only a good total (> 240 g/sqm) dose MTX but a serum peak over 1000 µmol/l at after 6 hours infusion or 1450 µmol/l after 4 hours infusion.