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Casos Clínicos

High-doses of methotrexate in osteosarcoma. Does it adjust to a real body surface area?

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SUMMARY
Case: 36 year-old male with body surface area of 2.44 m^2, diagnosed with osteosarcoma, treated with chemotherapeutic scheme based on methotrexate, cisplatin/ifosfamide and adriamycin. Methotrexate was not set according to the existing recommendations of limiting the total dose to 20 g or, adjusting it to 2 m^2, but 29.3 g (12 g/m^2) was prescribed. After receiving neoadjuvant chemotherapy and surgery, the tumor necrosis percentage was 91%. There are articles which support that a percentage of high tumor necrosis is associated with immediate levels above 1000 mcM, and that these in turn are correlated with a greater progression-free survival. In the above case, the results suggest that if the dose had been limited according to the cited recommendations, the tumor necrosis percentage would not exceed 90%.
Conclusions: The idiosyncrasy of each patient and the pharmacokinetics of each drug should be the factors that determine drug adjustment.

Key Words: **Patient safety, osteosarcoma, body surface area.**

Altas dosis de metotrexato en osteosarcoma. ¿Se ajusta a la superficie corporal real?

RESUMEN
Caso: Paciente de 36 años con una superficie corporal de 2,44 m^2, diagnosticado de osteosarcoma, tratado con un esquema basado en metotrexato, cisplatino, ifosfamida y adriamicina.
El metotrexato, es un fármaco que en ocasiones para su dosificación se limita la dosis a 2 m^2 de superficie corporal o a un máximo de 20 g, en este caso se dosificó a 12 g/m^2 sin limitación de dosis (29,3 g). Tras recibir quimioterapia neoadyuvante y cirugía el porcentaje de necrosis tumoral fue del 91%. Existen artículos en los que se correlaciona el porcentaje de necrosis tumoral con los niveles inmediatos superiores a 1000 mcM y esto a su vez, con una mayor supervivencia libre de progresión. En este caso, los resultados obtenidos sugieren que si en este paciente se hubiese limitado la dosis como referencian algunos protocolos el porcentaje de necrosis tumoral alcanzado podría haber sido inferior al 90%.
Conclusión: La idiosincrasia de cada paciente y la farmacocinética de cada fármaco debe ser el factor que determine el ajuste de dosis en cada ocasión.

Palabras clave: **Cuidado del paciente, osteosarcoma, superficie corporal.**

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INTRODUCTION

Drugs are mostly dosed according to the patient's weight, but there are exceptions. One is the case of cytostatics, which are usually dosed depending on body surface area (BSA)[1].

In oncology practice it is usual to dose drugs to a BSA of 2 m^2 in those patients with a BSA than this. This limitation is performed to avoid exposing patients to such high doses that they could produce more adverse effects related with dose. This accepted belief is not really documented in any publication, however, articles do exist that support that the use of the dose based on the actual weight of the patient, despite exceeding BSA=2 m^2, it does not increase adverse effects[1].

Osteosarcoma is a tumor that occurs primarily during the growing age and is more common in males[2], and it is located mainly in the metaphysis of long bones. The survival of patients with osteosarcoma has improved since the start of treatment with high-dose methotrexate (HDMTX)[3].

The efficacy of treatment with HDMTX, expressed on the basis of progression-free survival data, has been linked to a concentration at the end of infusion above 1000 mcM and an area under the curve (AUC) greater than 4000 mg*hr/L, while reducing the infusion time of the drug is recommended in the case of not reaching this maximum concentration[4]. Current figures place the overall survival of localized disease at 62% and 7% for those with disseminated disease (in a follow-up period of 123 months). In a subgroup analysis for patients with localized disease and degree of tumor necrosis >90% after neoadjuvant treatment, progression-free survival was 70%, whereas for those with a degree of tumor necrosis < 90% it was 44%[5].

Regarding safety, the toxicity profile of methotrexate (MTX) is associated with adverse effects at hematological, renal, liver, gastrointestinal and neurological. Hematological toxicity and mucositis have been related to sustained plasma levels of MTX rather than the peak reached[6].

DESCRIPTION OF CASE

A 36 year old male, was diagnosed in August 2013 with high grade osteosarcoma in the left distal femur, anatomical pathology refers to bone infiltration due to high grade sarcoma.

Anthropological data corresponded to 115 kg and 1,92 m in height (according to DuBois) that correspond to a 2,44 m^2 BSA. Creatinine clearance before beginning the protocol was 187 ml/min (according to Cockcroft-Gault).

The patient began neoadjuvant chemotherapy on 9th November with MTX 12 g/m^2, adriamycin 75 mg/m^2 (ADM) and cisplatin 90 mg/m^2 (CDDP). CDDP was modified by ifosfamide 3000 mg/m^2 (IFO) during the protocol as the patient had a sensorineural hearing loss. Finally, the scheme that followed was MTX (day +1), CDDP-ADM (+8), MTX (+32), MTX (+37), MTX (+44), IFO-ADM (+58), MTX (+78).

After these 7 cycles, surgery (+102) is performed.

Finally, he received adjuvant chemotherapy with MTX (+129), IFO-ADM (+140), MTX (+164), MTX (+172), IFO-ADM (+183) MTX (+204), MTX (+212), IFO-ADM (+223).

MTX was adjusted to 12 g/m^2 (without dose limitation for BSA or total dose) in a 4 hour infusion. MTX immediate plasma levels at 24 h, 42 h, the time until MTX plasma concentrations were <0.2 mcM and the obtained AUC are reported in table 1.

The Bayesian method implemented in Abbottbase Pharmacokinetics Systems (PKS) to predict plasma MTX concentration. MTX levels are considered at risk of toxicity when they are above, the following levels:

- $[MTX]_{24h} > 5$ mcM
- $[MTX]_{42h} \geq 1$ mcM

In these situations, rescue measures are intensified, such as the hyper-hydration (increase from 3 L/m^2 to 4,5 L/m^2), folinic acid rescues (increase rescue from 15 mg/m^2 to 500 mg/m^2) and urinary alkalinization. If the levels are too high, special measures are resorted to such as the use of activated charcoal, cholestyramine, carboxypeptidase and/or renal replacement techniques.

DISCUSSION

MTX is a drug from which it is possible to obtain plasma levels. This fact allows us to perform dose adjustment besides that carried out by the BSA[1], and thus to know what exposure the patient is undergoing, therefore adjusting the dose of subsequent cycles in cases in which they have not reached the desired levels[7]. Another feature of MTX is that rescues can be adjusted, with folinic acid, hydration and urinary alkalinization, managing to reverse intoxication in cases in which it was necessary.

After receiving the full treatment, the result of the anatomical pathology was: 8 cm high-grade osteosarcoma, limited to bone, tumor necrosis percentage of 91%, and resection margins free of neoplasia. There are articles[4,5] hat support that the percentage of tumor necrosis is associated with the immediate levels achieved. In our case we can observe that these levels obtained were within the range that is related to efficacy (>1000 mcM), and which in turn, correlate with a tumor necrosis percentage >90%.

At 42 hours, the levels obtained were not toxic, except the second cycle, in which they were slightly toxic, obtaining plasma levels of <0,2 mcM at 64 hours. In the first cycle reversible elevated hepatotoxicity of liver enzymes was shown, something relatively frequent in the use of MTX; at no time was any dose adjustment made.

Moreover, Fleming *et al.*[8] a studied that what is really important for dose adjustment of MTX is not the weight, but the renal function, as approximately 90% of the drug is eliminated this way.

All these reasons lead us to question what is collected in most osteosarcoma protocols, in which it is recommended to limit the total dose to 20 g or adjust the dose to 2 m^2 of maximum BSA for those patients with a BSA above this[5,9].

In the aforementioned case, the data suggest that if the dose had been limited to 20 g or BSA of 2 m^2 so as to try to avoid toxicity, a percentage of tumor necrosis above 90% would possibly have not been reached, as the outcome of the pathology was slightly higher with 91% tumor necrosis.

CONCLUSIONS

It would be interesting to perform studies in which patients in whom the dose is limited to 2 m^2 and in which they are dosed according to real-BSA are compared and check whether there are significant differences regarding effectiveness. On the other hand, it would be necessary to perform pharmacokinetic studies of drugs prior to recommending this limitation of the dose.

Each patient's idiosyncrasy and the pharmacokinetics of each drug should determine the dose adjustment.

Table 1
Methotrexate dose

Cycle Nº	Dose (g) [BSA] (m^2)	Plasma peak (mcM)	24h level (mcM)	42h level (mcM)	T <0,2 McM (h)	AUC mg*hr/L
1	29.3 [2.44]	1120	7.9	0,3 (46h)	50	3785
CDDP+ADM						
2	29.3 [2.44]	1640	17.6	3.6	64	5477
3	29.3 [2.44]	1550	11.6	0.6	53	4974
4	28.2 [2.35]	1602	11.3	0.7	58	4982
IFO+ADM						
5	28.8 [2.40]	2100	10.8	0.6	52	6316
SI	Tumor necrosis = 91%					
6	28.8 [2.40]	1450	15.1	0.6	51	5061
IFO+ADM						
7	28.8 [2.38]	1280	15.2	0.5	49	4211
8	28.8 [2.38]	1460	14.6	0.4(47h)	55	4915
IFO+ADM						
9	28.8 [2.40]	1050	16.4	0.9	55	4091
10	28.8 [2.44]	2100	21.4	0.6	66	6304
IFO+ADM						

ADM: adriamycin; BSA: body surface area; AUC: area under the curve; CDDP: cisplatin; IFO: ifosfamide; SI: surgical intervention.

Conflict of interest: The authors declare no conflicts of interest.

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