

Influence of Methotrexate Dose Intensity on Outcome of Patients with High Grade Osteogenic Osteosarcoma

Analysis of the Literature

Nicole Delepine, M.D.¹
 Gérard Delepine, M.D.²
 Gaetano Bacci, M.D.³
 Gerald Rosen, M.D.⁴
 Jean-Claude Desbois, M.D.¹

¹ Department of Paediatric Oncology, University Hôpital Robert Debré, Paris, France.

² Department of Orthopaedics, University Hôpital H. Mondor, Creteil, France.

³ Istituto Ortopedico Rizzoli, Centro Tumori Ossei Reperto di Chemioterapia, Bologna, Italy.

⁴ Cedars-Sinai Comprehensive Cancer Center, Los Angeles, California.

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Address for reprints: Nicole Delepine, M.D., Service Universitaire d'Oncologie Pédiatrique, Hôpital Robert Debré, 48 Boulevard Serurier, 75019 Paris, France.

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BACKGROUND. The authors surveyed the published clinical trial literature on the subject of localized high grade osteosarcoma in order to develop new hypotheses dealing with drug-dose combinations in the treatment of this disease.

METHODS. A computerized literature search was conducted to identify all available published reports of the clinical trials using high dose methotrexate (MTX) in multidrug protocols treating osteosarcoma. Thirty studies, including discussion of high dose MTX (> 7.5 g/m² per course) and precise quantification of 5-year disease free survival (DFS), fulfilled the inclusion criteria of this dose-intensity analysis. The total number of patients treated in eligible studies was 1909. Correlation among the planned total doses, the dose intensities of the drugs, and the 5-year DFS were tested by regression analysis.

RESULTS. No correlation of any other drug dose or dose intensity with DFS appeared as important as the MTX finding. In multivariate analysis, the dose intensity of MTX was found to be the one most correlated with DFS. This correlation appeared to hold for adjuvant and neoadjuvant trials.

CONCLUSIONS. The dose intensity of MTX seems to be a major factor in predicting the outcome of patients with localized high grade osteosarcoma. *Cancer* 1996; 78:2127–35. © 1996 American Cancer Society.

KEYWORDS: dose intensity, high dose methotrexate, cisplatin, doxorubicin, osteogenic osteosarcoma, clinical trials.

Before the use of chemotherapy, 80–90% of patients with nonmetastatic osteogenic sarcoma died despite early radical surgery.^{1–4} With the use of multidrug chemotherapy, approximately two thirds of patients with nonmetastatic resectable primary tumors can be cured.^{5–12} This improved outcome has been attributed, in part, to the use of high dose methotrexate (MTX) with leucovorin rescue as described by Jaffe et al.^{13–15} and emphasized by Rosen et al.^{16–18}

Although high dose MTX was the most commonly used drug to treat this tumor, there was no consensus on the best MTX dosage or on the real impact of dose intensity of MTX on disease free survival (DFS) of patients with osteosarcoma. Of three randomized trials that have tested the superiority of higher doses of MTX over low or moderate doses, one monocentric study showed a significant difference¹⁹ and another did not.²⁰

Evidence of the importance of dose intensity in improving survival after multidrug chemotherapy has been identified for both adult and paediatric patients with solid tumors^{21,22} and hematologic diseases.²³

Because high dose MTX therapy is costly, time consuming, and potentially dangerous, the benefit of high doses should be clearly

TABLE 1
Validated Data

	Reference	No. of patients	Length (wk)	Dose MTX (g/m ²)	Dose DOXO (mg/m ²)	Dose CDDP (mg/m ²)	Dose CPX (mg/m ²)	5-yr DFS (%)
EIO 80861 MTX	25	195	20	96	360	400	0	45
MIOS	26, 27	165	45	144	380	400	6000	63
CCG 782 BR	28	117	45	80	450	540	6000	50
Rizzoli 2 GR	5	117	30	40	480	600	0	71
Rizzoli 2 BR	5	47	40	40	480	600	0	57
EIO 80831 MTX	6	99	18	32	300	400	0	41
CCG 741	28	83	72	90	570	0	0	37
SSG BR	10	80	43	64	450	720	6000	53
COSS 77	11, 29	68	52	102	450	0	7200	50
EORTC 20781	2	68	41	42	420	0	6000	24
Rizzoli 1 high dose MTX	19	67	31	37.5	480	600	0	58
Rosen T10 BR	9	59	46	140	450	720	4800	71
Rosen T10 GR	9	57	42	240	360	0	4800	92
COSS 80 BCD	11, 29	56	33	168	360	0	4800	65
CCG 782 GR	28	55	40	144	360	0	6000	80
SFOP BR	7	65	43	70	450	720	4800	42
Rosen T4	17, 18	52	40	120	540	0	4800	48
SFOP GR	7	40	40	190	360	0	4800	76
Dana Farber 3	30, 31	46	52	180	450	0	0	59
COSS 80 CDDP	11, 29	45	33	168	360	480	0	66
Rosen T12 BR	32	44	29	72	360	480	4800	56
COSS 82 BCD BR	12, 29	40	26	48	360	540	2400	39
Rosen T7 GR	18	40	42	240	360	0	4800	95
Florida A	33	37	52	52	280	700	0	48
IGR T10 GR	8	33	40	176	360	0	4800	75
Rosen T 12 GR	32	32	16	96	240	0	4000	83
COSS 82 DOXO GR	12, 29	31	22	96	240	420	0	74
IGR T10 BR	8	27	43	88	450	720	4800	50
Dana Farber 2	30, 31	24	52	180	450	0	0	50
COSS 82 DOXO BR	12, 29	20	25	48	120	525	3600	57

MTX: methotrexate; DOXO: doxorubicin; CDDP: cisplatin; CPX: cyclophosphamide; DFS: disease free survival; EIO: European Intergroup for Osteosarcoma; MIOS: Multi-Institutional Osteosarcoma Study; CCG: Children's Cancer Group; BR: bad responders; GR: good responders; SSG: Scandinavian Sarcoma Group; COSS: Co-operative Osteosarcoma Study; EORTC: European Organization for Research and Treatment of Cancer; SFOP: Société Française d'Oncologie Pédiatrique; IGR: Institut Gustave Roussy.

documented. Hoping to clarify the situation, we undertook a dose-intensity analysis of multiagent chemotherapy of primary nonmetastatic limb osteosarcoma. We were interested in determining if this method of analysis could identify the contribution of each agent to patient outcome and, particularly, if better DFS is significantly associated with higher dose or/and higher dose intensity of MTX, doxorubicin, cisplatin, or cyclophosphamide.

METHODS

Literature Assembly

A computerized literature search encompassing January 1976 to March 1995 was conducted to identify all available published reports of clinical trials using MTX in treating osteosarcoma. This search was supplemented by a systematic examination of citations in all retrieved articles and major congress abstracts. Cita-

tions were searched using the subject headings of osteosarcoma and/or MTX, limited to Western languages. All reports were reviewed to see if they matched the inclusion criteria.

Published data were then analyzed to evaluate the association of dose intensity of MTX with favorable patient outcome.

Inclusion Criteria

Only those studies that fulfilled the following criteria were included.

1. Stage II limb osteosarcoma (primary, high grade, non-metastatic) in patients younger than 40 years of age.
2. At least 30 patients included in the study, and at least 20 patients treated on the same chemotherapy regimen when the protocol used different regimens (for instance, for good and bad responders).

TABLE 2
Calculated Data

	Reference	MTX DI (g/m ² /wk)	DOXO DI (mg/m ² /wk)	CDDP DI (mg/m ² /wk)	Length (wk)	5-yr DFS (%)
EIO 80861 MTX	25	4.8	18	8.88	20	45
MIOS	26, 27	3.2	8.44	12	45	63
CCG 782 BR	28	1.77	10	20	45	50
Rizzoli 2 GR	5	1.33	16	15	30	71
Rizzoli 2 BR	5	1	12	22.2	40	57
EIO 80831 MTX	6	1.77	16.67	22.2	18	41
CCG 741	28	1.25	7.91	16.74	72	37
SSG BR	10	1.48	10.46	0	43	53
COSS 77	11, 29	1.96	8.65	0	52	50
EORTC 20781	2	1.02	10.24	19.35	41	24
Rizzoli 1 high dose MTX	19	1.20	15.48	16.74	31	58
Rosen T10 BR	9	3.04	9.78	15.6	46	71
Rosen T10 GR	9	5.71	8.57	0	42	92
COSS 80 BCD	11, 29	5.09	10.9	0	33	65
CCG 782 GR	28	3.6	9	0	40	80
SFOP BR	7	1.62	9.78	16.74	43	42
Rosen T4	17, 18	3	13.5	0	40	48
SFOP GR	7	4.75	9	0	40	76
Dana Farber 3	30, 31	3.46	8.65	0	52	59
COSS 80 CDDP	11, 29	5.09	10.9	14.55	33	66
Rosen T12 BR	32	2.48	12.41	16.55	29	56
COSS 82 BCD BR	12, 29	1.84	13.84	20.77	26	39
Rosen T7 GR	18	5.71	8.57	0	42	95
Florida A	33	1	5.38	13.46	52	48
IGR T10 GR	8	4.4	9	0	40	75
Rosen T 12 GR	32	6	15	0	16	83
COSS 82 DOXO GR	12, 29	4.36	10.9	19.09	22	74
IGR T10 BR	8	2.04	10.46	16.74	43	32
Dana Farber 2	30, 31	3.46	8.65	0	52	50
COSS 82 DOXO BR	12, 29	1.92	4.8	21	25	57

DI: dose intensity; MTX: methotrexate; DOXO: doxorubicin; CDDP: cisplatin; DFS: disease free survival; EIO: European Intergroup for Osteosarcoma; MIOS: Multi-Institutional Osteosarcoma Study; CCG: Children's Cancer Group; BR: bad responders; GR: good responders; SSG: Scandinavian Sarcoma Group; COSS: Co-operative Osteosarcoma Study; EORTC: European Organization for Research and Treatment of Cancer; SFOP: Société Française d'Oncologie Pédiatrique; IGR: Institut Gustave Roussy.

- Multidrug chemotherapy including high dose MTX (≥ 7.5 g/m² per course).
- Chemotherapy treatments with the dose and schedule clearly specified for good and bad responders, sufficient to allow calculation of the planned dose intensity of each drug of the protocol.
- Clear quantification of 5-year DFS of patients in each treatment arm.

Studies were excluded if the information was incomplete and could not be completed by letter inquiries to the first author, if the follow-up time was too short, or if the treatment was not uniform for the patients studied.

In several instances, the result of a single clinical trial was reported in more than one article. For these trials, we used the most comprehensive publication to analyze the treatment protocol and calculate the dose intensities; we used the latest report to obtain the 5-

year DFS rate and the total number of patients included.

Criteria for Measuring Effect of Treatment

We used the 5-year DFS percentage for end-point analysis. This end point was preferred to histologic response because it takes into account the effect of the whole treatment, permits the consideration of neo-adjuvant and adjuvant protocols, is provided in most series, and less than 5% of relapses appear after this period, making this figure a good indicator of the cure rate.

Dose Intensities Calculations

Two critical assumptions used in the analysis were that primary nonmetastatic osteosarcoma of the limb is a homogeneous group and that imbalances in the population characteristics among clinical trials were

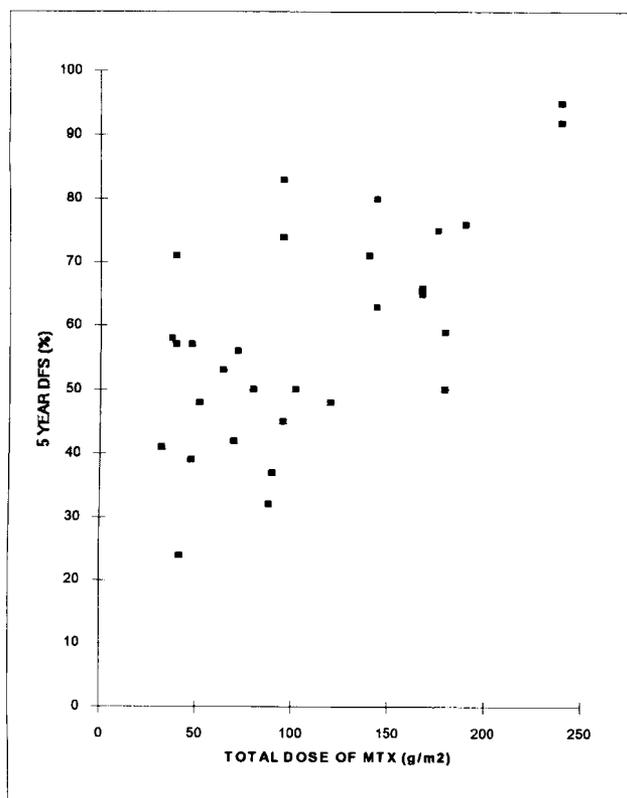


FIGURE 1. Correlation between 5-year disease free survival and total dose of methotrexate ($P < 0.05$).

unimportant. These were reasonable assumptions because in a recent comprehensive study,²⁴ no significant prognostic factors were found to differentiate subgroups of different curability among these patients (except primary metastases and trunk location, which were excluded in this study).

As in other previous analyses of dose intensity, the schedule dependence was not considered.

We wished to establish a hypothesis linking patient outcome with drug intensity. The projected intensity of each drug was calculated by dividing the total planned dose (as grams per square meter for MTX and cyclophosphamide, and as milligrams per square meter for the other drugs) for the entire regimen by the duration (in weeks) of the entire treatment. DFS was defined as the duration in months from diagnosis to the time the patient relapsed or the time of last follow up.

Statistical Analysis

To identify the most plausible hypothesis for future testing, we used simple linear regression analysis to screen the dose-related variables for relationship with DFS. The variables included in this phase of explor-

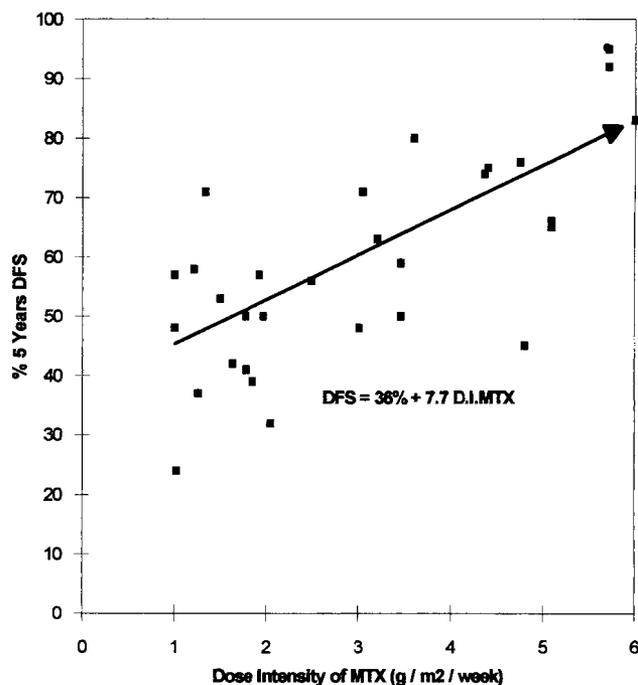


FIGURE 2. Correlation between 5-year disease free survival and dose intensity of methotrexate ($P < 0.05$).

atory analysis were the total planned dose and the planned dose intensity of each drug, the total duration of treatment, the number of patients included, the year the study began, the final publication of the study, and the eventual interfactor correlation. Of these variables, total planned dose and the dose intensity of MTX appeared to be correlated with DFS.

The second phase of the exploratory analysis involved multivariate analysis to determine likely relationships with DFS given the possible intracorrelations among the variables. The variables included were the total planned dose and the planned dose intensity of each drug. The method of weighted least squares where the weights were the number of patients, in each trial, was used to calculate coefficients for the regression model.

To provide a visual representation of the regression, we have included partial regression graphs in plotting DFS rate versus the dose intensity of the significant drugs. The partial regression plot for a DFS rate (y) and a variable (x) not included in a regression model containing a predictor MTX is defined in the following way. The vertical axis (DFS residual) represents the difference between the observed DFS rate and the DFS rate predicted from the regression model containing the predictor (dose intensity of MTX). The horizontal axis represents that part of variability in variable x not correlated with the predictor already in

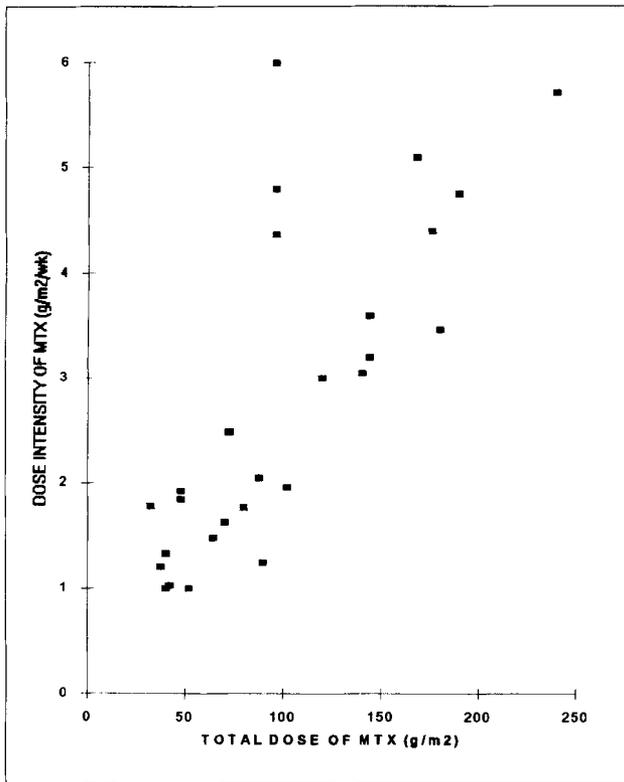


FIGURE 3. Correlation between total dose and dose intensity of methotrexate ($P < 0.05$).

the regression model. Therefore, the partial regression graph eliminates the effect of correlation between predictors included in the model and the variable x .

RESULTS

Validated Data

A total of 61 clinical treatment arms using high dose MTX for osteosarcoma were identified; 31 were excluded because of our selection criteria. The 30 studies included were 10 monocentric studies (Rosen's T4, T7, T10, and T12; Dana Farber 2 and 3; Rizzoli 1 and 2; Gustave Roussy Institute's T10; Florida A studies) and 10 multicentric randomized trials (Multi-Institutional Osteosarcoma Study; Austrian-German Co-operative Osteosarcoma Study (COSS) 77, 80, and 82; European Organisation for Research on Treatment of Cancer 20781; European Intergroup 80831 and 80861; Scandinavian Sarcoma Group's T10; Children's Cancer Group 741 and 782). These 30 studies met our inclusion criteria and are summarized in Table 1. The total number of patients treated in eligible studies was 1909. The duration of chemotherapy regimens ranged from 16 to 72 weeks, the total planned dose of MTX from 32 to 240 g/m², the dose of doxorubicin from 120 to

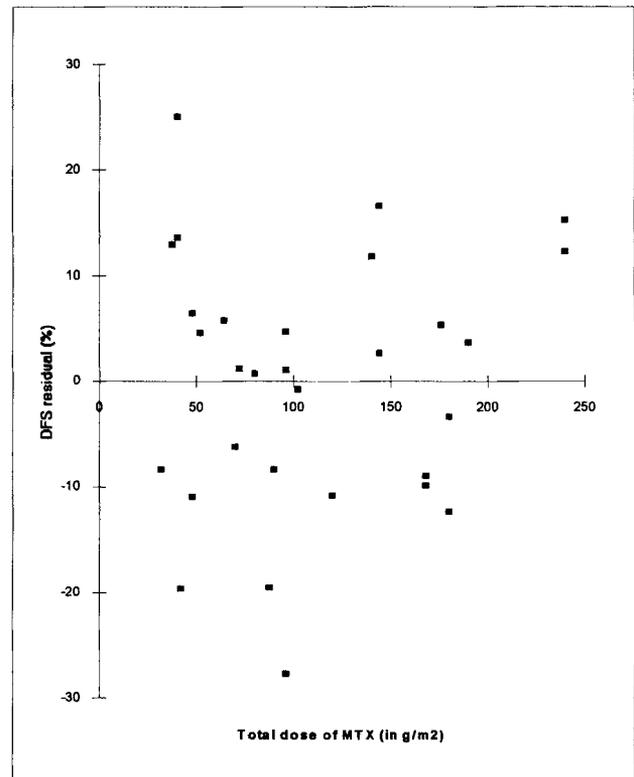


FIGURE 4. After adjustment for dose intensity of methotrexate, the total dose of methotrexate is not correlated with disease free survival.

570 mg/m², the dose of cisplatin from 0 to 720 mg/m², the dose of cyclophosphamide from 0 to 7200 mg/m², the dose intensity of MTX from 1 to 6 g/m²/wk, the dose intensity of doxorubicin from 4.8 to 18 mg/m²/wk, the dose intensity of cisplatin from 0 to 22 mg/m²/wk, the dose intensity of cyclophosphamide from 0 to 144 mg/m²/wk, and the 5-year DFS rates from 24 to 95% (Tables 1 and 2).

Most patients underwent primary chemotherapy based on MTX, surgical resection of the primary or an amputation, and multidrug postoperative chemotherapy.

Univariate Analysis

Based on the univariate analysis, we observed that the planned total dose of MTX (Fig. 1) and the planned dose intensity of MTX (Fig. 2) have both a significant influence ($P < 0.05$) on DFS and are significantly correlated together ($P < 0.05$) (Fig. 3).

Conversely, the planned doses and planned dose intensities of all other drugs (doxorubicin, cisplatin, cyclophosphamide), patient age, patient sex, number of patients included in each study, inclusion time period, monocentric or multicentric design, randomized

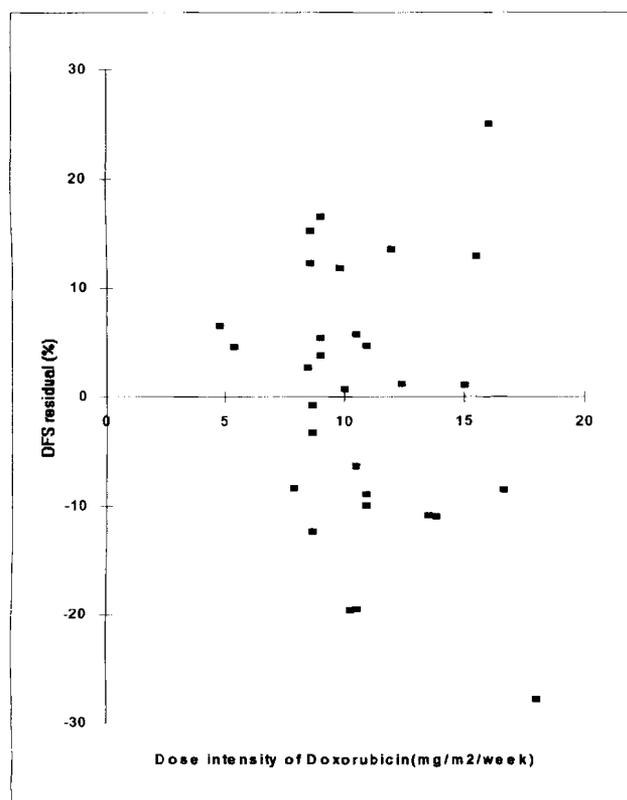


FIGURE 5. After adjustment for dose intensity of methotrexate, the dose intensity of doxorubicin is not correlated with disease free survival.

or historic design, and total duration of the protocols had no significant impact on DFS.

Multivariate Analysis

In multivariate analysis, the planned dose of MTX did not have a significant impact on the clinical outcome, as shown on the partial regression graphs plotting the DFS residual rate versus the dose residual of MTX (Fig. 4). The dose intensity of MTX remains the only independent factor significantly correlated with DFS ($P < 0.05$). In subgroups analysis, the correlation between the dose intensity of MTX and DFS is significant for adjuvant and neoadjuvant protocols as well as for good and bad responders to preoperative chemotherapy. The correlation between the dose intensity of MTX and DFS of good responders to preoperative chemotherapy is highly significant, as seems logical. However, a significant correlation ($P < 0.05$) between the dose intensity of MTX and DFS in patients whose tumor showed a bad histologic response to preoperative MTX was also found.

Except for dose intensity of MTX, the comprehensive regression analysis could not demonstrate any significant correlation between planned dose or dose in-

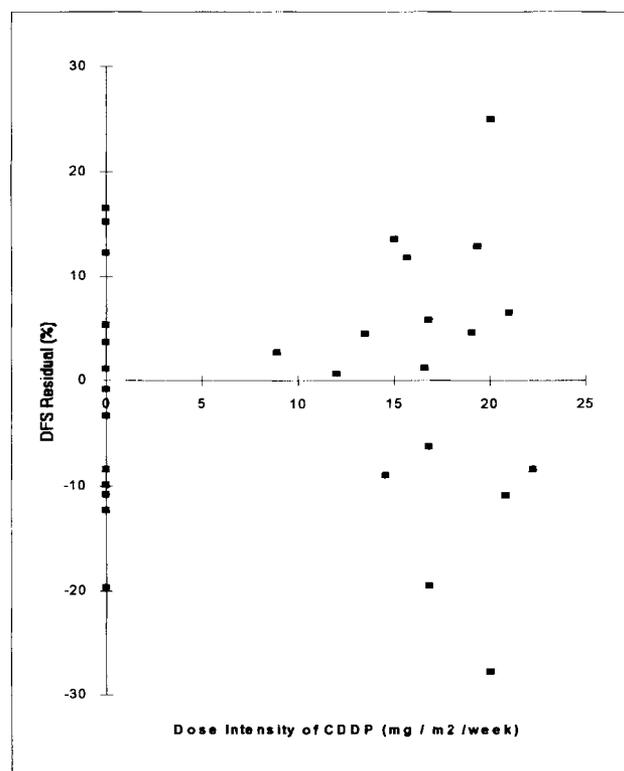


FIGURE 6. After adjustment for dose intensity of methotrexate, the dose intensity of cisplatin is not correlated with disease free survival.

tensity of any drug and outcome of patients. The absence of correlation between dose intensity of the significant drugs is illustrated by the partial regression graphs in plotting DFS rate versus the dose intensity of doxorubicin (Fig. 5) and cisplatin (Fig. 6).

In view of the likelihood of the use of multiple agents in recent versus earlier studies, as well as the improvements in supportive care, an adjustment for the period over which these studies were conducted was also considered. After adjusting for dose intensity of MTX, these period variables (year the trial began, year the trial ended, and year the trial was published) did not contribute significantly to the prognosis.

We were also concerned that the small single institution studies, which tended to be the more aggressive ones, were especially susceptible to publication bias; however, in those data sets, there was no correlation between sample size of trials and outcome of patients.

DISCUSSION

Limits of this Analysis

This report provides results of a survey of 61 published clinical trial regimens used to treat 1909 patients with high grade localized osteosarcoma. The purpose of the study was to develop a new hypothesis involving the

chemotherapy agents that had been included in published studies. This in-depth survey of the agents and their impact on DFS was considered important in clarifying design and purpose of future clinical trials. Our intent has been accomplished by the finding that high dose MTX should be considered using the dose-intensity measure described in this article. We suggest that dose-intense MTX be considered with other dose-intense chemotherapy agents in new randomized clinical trials. Our findings suggest that DFS might be improved by 20%. The hypothesis might be tested by comparing a dose-intense regimen versus the total dose of the same agents or, alternatively, two different combinations of dose-intense agents.

Numerous limits of this study must be taken into account. Some are inherent to the dose-intensity analysis concept, others to the retrospective screening of our data, and finally to the available drug associations during the screened period.

As usual in dose-intensity analysis, our study ignores scheduling, interdrug synergy, and interpatient pharmacokinetic variability. MTX is nevertheless one of the drugs for which synergy is indisputable^{34,35} and one with the highest interpatient pharmacokinetic variability.³⁶⁻³⁸ This literature review gives only one key to the problem and needs to be completed and refined by a MTX concentration \times time curve/prognosis analysis³⁹⁻⁴¹ that we could not perform in this study due to a lack of data.

Our retrospective analysis includes studies from treatment centers around the world over the past 25 years. Because our analysis was retrospective and used published, nonrandomized clinical trials, it was expected that external factors (e.g., the difference between intended and received dose, the variability of MTX infusion-hydration protocols, the refinement of diagnostic studies for assessing relapse, and the introduction of new effective treatment and supportive care) would greatly weaken the comparability of these published studies. Despite improvements in staging methodologies, the incidence of stage II osteosarcoma has remained stable, suggesting that "stage migration" could not have accounted for the better treatment results over the years, and no independent correlation could be found between the time period of studies and DFS of patients.

The highly significant positive association of dose intensification of MTX with higher DFS is particularly striking considering the number of cytotoxic agents used in these regimens. One reason could be the very large range of MTX dose intensities observed (1 to 6 g/m²/wk). Some limits in the analysis of the role of other drugs must be underlined. All trials included doxorubicin with comparable doses; for that reason,

the conclusions of our study fully apply only to doxorubicin containing regimens. The relatively small range of intensities does not permit a precise statement about the importance of this drug already established in German,²⁹ American,⁴²⁻⁴⁴ and Italian⁴⁵ studies. The design of the study does not permit the assessment of the role of cisplatin. Only half the studies used cisplatin, and in most cases only for salvage of bad responders. The number of these studies is too low to permit subgroup analysis. Ifosfamide is a major drug for osteosarcoma and has been included in most recent protocols, but the results of these protocols are not yet published with 5-year follow up and could not be considered in this study. The influence of this promising drug may affect results in the future.

Comparison with Other Studies

In a recent dose-intensities analysis, Smith et al⁴² did not find any influence of MTX dose intensity on the response of osteosarcoma to preoperative chemotherapy. However, their study calculated the dose intensity of MTX by the number of courses per time unit and did not consider the real dose itself. The choice of the histologic response as the end point in their study (instead of late DFS, as in the current study) allowed the authors to take only the preoperative phase of treatment into account. It assumes that the chemosensitivity of the primary is always a reliable marker of the chemosensitivity of lung micrometastases, regardless of the nature and duration of the administration of the drug and of the postoperative treatment; this is an assumption that nobody can prove. In this study, the significant correlation between the dose intensity of MTX and outcome of bad responders suggests that the microscopic disseminated disease could better respond to MTX than the primary, as already advocated by Rosen, Nirenberg.⁴⁶ It also suggests that bad prognosis of bad responders could be worsened by stopping MTX too early, resulting in a dose intensity of this drug that is too low.

Our observation of the association of higher MTX dose intensity with favorable outcome follows the previously recognized improvements in the outcome for patients receiving higher doses of MTX in Rosen's T4 and T7, COSS's 77 and 80, and Rizzoli 1 protocols.

The primary result of the Rizzoli 1 study¹⁹ was the substantial improvement of survival for patients treated with high dose MTX (7.5 g/m²) compared with that of patients treated with a lower dose (0.75 g/m²); the dose intensity of the high dose MTX treatment arm was relatively low (1.2 g/m²/wk) and was associated with a 5-year relapse free survival rate of 58%, compared with 44% for the lower dose treatment arm. Thus, the Rizzoli 1 study demonstrated that a moder-

ate MTX dose intensity improves survival compared with a dose that is too low ($0.12 \text{ g/m}^2/\text{wk}$).

The major progress in DFS of children treated by Rosen's T4-T5 and T7 correlated strongly with the increase of dose intensity of MTX from $3 \text{ g/m}^2/\text{wk}$ ($6 \text{ g/m}^2/\text{course}$) to $5.7 \text{ g/m}^2/\text{week}$ (8 to 12 g/m^2 per course). The worst results of Rosen's T12 and T14 compared with T7 and T10 follow the decreasing of MTX dose from $5.7 \text{ g/m}^2/\text{wk}$ to 2.4 to $3.2 \text{ g/m}^2/\text{wk}$.

Similar findings appeared in the German-Austrian multicentric randomized studies when analyzing results of COSS 77, COSS 80, and COSS 82 by MTX dose intensity. Increasing the dose intensity of MTX from $1.85 \text{ g/m}^2/\text{wk}$ (COSS 82, bleomycin, cyclophosphamide, dactinomycin (BCD) treatment arm, bad responders) and $1.96 \text{ g/m}^2/\text{wk}$ (COSS 77) to more than $5 \text{ g/m}^2/\text{wk}$ (COSS 80 BCD or cisplatin and COSS 82, BCD treatment arm, good responders) resulted in higher life expectancy—from 39 to 65%.

The relative failure of the Scandinavian Sarcoma Group to reproduce Rosen's T10 results can, in part, be related to the lower dose intensity of MTX in patients aged 8 to 12 years. In Rosen's studies T7 and T10, these children received $12 \text{ g/m}^2/\text{course}$ compared with 8 g/m^2 in the Scandinavian study.

In summary, in monocentric, multicentric, pilot, or randomized studies, the dose intensity of MTX correlates strongly with DFS. Although such analysis could not establish a causal relationship between dose intensity of MTX and patient DFS, they certainly identify a clinical variable of great prognostic significance.

CONCLUSIONS AND IMPLICATIONS IN DESIGNING CHEMOTHERAPY PROTOCOLS FOR OSTEOSARCOMA

The ultimate goal of all therapeutic trials is to increase the cure rate of patients. In most recently published studies on osteosarcoma, the interest of investigators was too often focused on the response of the primary tumor to preoperative chemotherapy, doxorubicin, and platinum, rather than delivered drug intensities analyses and defining the central role of MTX. Most agents active on osteosarcoma cannot be increased to more than twice the conventional dose because of limiting bone marrow and extramedullary toxicity.

Although maximizing MTX dose intensity has a significant effect on clinical outcome, toxicity is not a major limiting factor.^{9,32,46} With leucovorin rescue and pharmacokinetic monitoring, escalating the dose of MTX per course permits an increase in the dose intensity of this drug, usually without significant delay in protocol and without a notable decrease of the intensities of other active, more myelotoxic drugs. This study suggests that such an escalating dosage should in-

crease DFS significantly and confirms what we observed in our patients.⁴⁷

Despite very aggressive salvage chemotherapy, the prognosis of bad responders still remains poor. This study argues for maintaining MTX and adding a new drug (ifosfamide) to MTX, instead of early cessation of MTX. The results of the very few protocols that tried such an approach^{5,47,48} are promising for initial bad responders.

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