

# HIGH-DOSE METHOTREXATE WITH LEUCOVORIN RESCUE IN OSTEOSARCOMA: THE BEGINNING OF THE ODYSSEY

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## INTRODUCTION

Osteosarcoma is the most frequently encountered malignant bone tumor in the pediatric population<sup>(1)</sup>. It has a peak occurrence in the second and third decades of life. Before the 1970's, the cure rate for localized tumors was less than 20%<sup>(2)</sup>. The tumor was originally considered chemoresistant and was usually treated by amputation. However, despite this mutilating procedure, the majority of the patients eventually died from pulmonary metastases which usually appeared six to nine months after the operation. These metastases, at diagnosis, were not detected on routine conventional chest radiographs or tomography. Computerized axial tomography (CT scan) which became available later also did not produce any substantial increase in the detection of metastases. Based upon this observation, it was surmised that invasion by pulmonary micrometastases was present in 80% of patients at the time of diagnosis<sup>(3)</sup>. This concept was bolstered by a review of approximately 400 osteosarcoma patients treated at the Children's Cancer Research Foundation in Boston and also by a review of the literature in which the clinical features of more than one thousand cases of osteosarcoma were recorded<sup>(2)</sup>.

Recognition of the pre-existence of pulmonary metastases in the majority of patients at diagnosis lead to the conclusion that osteosarcoma had to be considered a systemic disease and that systemic treatment would be required to achieve cure. Unfortunately, prior to the 1970's, this goal could not be realized: there was virtually no systemic chemotherapeutic agent which was effective against the disease<sup>(2),(4)</sup>. Treatment resided principally in amputation. Radiation therapy delivered to the primary tumor and lungs had also been attempted, but was not curative.

## HIGH DOSE METHOTREXATE

In the early 1970's, two chemotherapeutic agents were found to be active in osteosarcoma. These comprised Adriamycin<sup>(5)</sup> and high-dose Methotrexate with Citrovorum factor «rescue» (Leukovorin «rescue»)<sup>(6)</sup>. The efficacy of the agents was demonstrated against overt metastatic disease.

High-dose Methotrexate with Leukovorin rescue was initially administered on a three-weekly cycle at a dose of 250 mg/kg or 7.5 gm/m<sup>2</sup>. Subsequent investigations revealed that the treatment was predominantly non-myelosuppressive. It was therefore administered on a weekly basis and was found to be highly effective<sup>(7)</sup>. Additional investigations also revealed that it could potentiate the action of radiation therapy<sup>(8)</sup>. In this capacity, while not curative, it was found to be extremely useful as a palliative maneuver.

The responses attained with high dose Methotrexate provided the impetus to administer the agent as adjuvant treatment after surgical ablation of the primary tumor<sup>(3)</sup>. The intent was to destroy the pulmonary micrometastases. In this context, it was administered alone and in combination with other agents. The strategy proved successful and produced a three-year disease-free survival of 50 to 80%<sup>(9)</sup>. This was statistically significant when compared to survival in historical controls, which in optimum circumstances, was approximately 20%.

## CONTROVERSY

Unfortunately, the contention that improved survival could be attributed to chemotherapy did not go unchallenged<sup>(10), (11), (12)</sup>. The Mayo Clinic adduced data to suggest that there had been a «natural» improvement in survival over several years and that it was not necessary to assume that chemotherapy, particularly high dose Methotrexate, was responsible for the improvement<sup>(13), (14)</sup>. Thus, prior to 1969, according to the Mayo Clinic data, survival had indeed remained constant at about 20%. This was consistent with historical controls. However, between 1969 and 1972, a trend toward improved survival was apparent and between 1972 and 1974, survival with amputation alone was as high as 40%<sup>(14)</sup>. This observation was later supported by a randomized trial in which surgery and high dose Methotrexate were compared to a concurrent treatment arm of surgery only. The study failed to demonstrate any advantage with high dose Methotrexate: survival in both arms was approximately 40%<sup>(15)</sup>. The observation made by the Mayo Clinic also received additional support from other investigators<sup>(16), (17)</sup>. During this period, claims and counter claims were made and the validity of historical controls was impugned<sup>(17), (18), (19), (20), (21), (22)</sup>. It was also suggested that recent improved diagnostic techniques, particularly CT scanning, could possibly have identified patients with pulmonary metastases and, when compared to historical controls, had altered the characteristics of the study population undergoing treatment with adjuvant chemotherapy<sup>(17)</sup>. As a consequence, treatment had been administered to, and successful results claimed for, a substantial number of patients who were intrinsically free, and would remain free, of pulmonary metastases. The concept is known as «Stage Migration» and was designated «The Will Rogers Phenomenon»<sup>(23)</sup>.

## REBUTTAL

Support for the efficacy of high-dose Methotrexate, remained steadfast by its advocate<sup>(9), (19), (20), (24)</sup>. This was based upon a number of factors: 1) It was demonstrated that the survival of patients with osteosarcoma treated with amputation prior to the 1970's had remained constant, i.e. approximately 20% in optimum circumstances<sup>(2), (9)</sup>. 2) The possibility of a «spontaneous» (improved) survival emerging over several consecutive years in the historical context series as reported by the Mayo Clinic was challenged. This could not be substantiated in the historical control series published by the M. D. Anderson Cancer Center<sup>(25)</sup>, the Dana Farber Cancer Center<sup>(26)</sup> and the Memorial Sloan-Kettering Cancer Center<sup>(27)</sup>. 3) The improved survival reported by the Mayo Clinic had included several groups of patients who had received a variety of adjuvant regimens in addition to surgery<sup>(13)</sup>. 4) Statistical computations were available to compensate for and adjust differences when comparing historical control patients with current studies<sup>(28)</sup>. 5) The contention that CT scans of the lung could invalidate historical controls was refuted. Improved

detection of metastases by this means was apparently not vastly superior to the results obtained by conventional radiographs. For example, in two reported studies it varied from 1.9% to 9.3%<sup>(29)</sup>,<sup>(30)</sup>. 6) A counter argument to the Stage Migration concept was the possibility that chemotherapy, in the absence of CT scans, had also been administered to patients with undetected (overt) pulmonary metastases and such patients had been rendered free of disease. 7) Finally, although «natural» biologic changes could influence the outcome of individual patients, such biologic variables had not been substantiated and assumed less significance when similar or identical results were being widely (and independently) reported.

## RESOLUTION

The foregoing dispute eventually led to the contention that clinical trials with concurrent controls (as opposed to historical controls) would be necessary to confirm the stated efficacy of adjuvant chemotherapy (particularly high-dose Methotrexate) in osteosarcoma. It was therefore elected to conduct a multi-institutional osteosarcoma trial, utilizing the chemotherapeutic regimen claimed to be the most effective at that particular time. The objective was to determine whether intensive multi-agent chemotherapy, administered as adjuvant treatment after ablation of the primary tumor, would significantly improve disease-free survival in non-metastatic patients with tumors of the extremity<sup>(31)</sup>. As a comparison, a «concurrent» control series of patients would be randomized to treatment with surgery only. This decision proved particularly ascerbic to investigators who had witnessed the efficacy of chemotherapy.

## RESULT OF THE MULTI-INSTITUTIONAL OSTEOSARCOMA TRIAL

Patients treated with surgery and adjuvant postoperative chemotherapy achieved a 66% two-year disease-free survival<sup>(31)</sup>. This was similar to the reported results attained with adjuvant chemotherapy. In contrast, patients treated with surgery only, garnered a significantly worse outcome: under 20% survival<sup>(31)</sup>. This was comparable to survival in the historical control series<sup>(2), (3), (25), (26), (27)</sup>. The inference of the study was clear: chemotherapy was effective and the historical control series were valid. Subsequently, a similar investigation by Eilber utilizing concurrent randomized controls, endorsed this finding<sup>(32)</sup>. An editorial by Holland depicted the opprobrium in investigators opposed to the concurrent randomized trial incorporating a no treatment chemotherapy arm<sup>(33)</sup>.

## ADDITIONAL STUDIES WITH HIGH DOSE METHOTREXATE

In the intervening period, investigators, unencumbered by the concurrent randomized trial, demonstrated that high-dose Methotrexate was also effective in the treatment of the primary tumor<sup>(34)</sup>. (A subsequent randomized comparative study, however, revealed that it was not as efficacious as cis-diamminedichloroplatinum-II when utilized for this purpose<sup>(35)</sup>.) Notwithstanding, Further studies also demonstrated that similar responses could be achieved when Methotrexate was administered in the same dose and schedule by the intra-arterial or intravenous route<sup>(36)</sup>. This suggested that a critical (finite) Methotrexate dose was required to achieve a

successful result. Any escalation above this dose apparently would not enhance therapeutic efficacy: 7.5 g/m<sup>2</sup> appeared to be appropriate, but in order to insure adequate tumoricidal concentrations, doses of 12 - 12.5 g/m<sup>2</sup> were selected<sup>(34), (35), (36), (37), (38)</sup>. The optimum effect was possibly attained with serum minimum concentration of 1,000 µmole/L at the end of a six-hour infusion. More recent studies also suggested that it would be important to adjust the dose according to the individual patient's pharmacokinetic profile<sup>(38), (39)</sup>.

## CONCLUSION

High dose Methotrexate with Leucovorin rescue is a functional regimen. Its acceptance into the therapeutic armamentarium for osteosarcoma was initially marred by controversy. Despite its discovery approximately 30 years ago, and numerous reports outlining its efficacy, the optimum method of its administration remains to be determined. Its non-myelosuppressive properties make it ideal to administer in combination regimens. Factors influencing its activity include patient age, pharmacodynamics, and tumor histology. The saga and utility of Methotrexate in osteosarcoma constitute a challenge to the new millenium: The odyssey must continue.

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