A Controlled Pilot Study of High-Dose Methotrexate as Postsurgical Adjuvant Treatment for Primary Osteosarcoma

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Thirty-eight patients whose primary extremity or limb girdle osteosarcomas had been completely excised (37 amputations, one limb sparing procedure) were allocated at random to two treatment groups receiving respectively regular follow-up examinations plus a high-dose methotrexate (HDMTX) regimen or regular follow-up without primary adjuvant chemotherapy. Although the vincristine, HDMTX, leucovorin regimen was generally quite tolerable when given at three-week intervals for one year and most of the chemotherapy patients followed the planned HDMTX dose escalations from 3 to 6 to 7.5 g/m^2, delayed methotrexate excretion limited dosage escalations in 25%. An estimated 52% of the 38 patients were surviving five years after randomization and an estimated 42% remained continuously relapse-free after five years. No significant differences between the outcomes of the 20 treated and the 18 untreated patients were apparent; however, power to detect differences was low. Furthermore, no significant differences in postmetastasis survival were apparent between the 12 treated and 10 untreated patients who relapsed. Approximately 20% of these failing patients appear to have been salvaged for long-term survival. This pilot study of HDMTX confirms the continuing need for controlled clinical trials in determining the therapeutic value of adjuvant chemotherapy programs for patients with primary osteosarcoma.

ALTHOUGH osteosarcoma is a distinctly uncommon disease, its proper treatment has been the topic of much discussion during the past decade.[1-3] It had long been recognized as a rather drug-resistant cancer for which little could be done except prompt ablative surgery, when in 1974 new hope arose with the simultaneous publication of two strongly positive adjuvant chemotherapy reports.[4, 5] Other encouraging reports followed rapidly, and both high-dose methotrexate (HDMTX) and doxorubicin were widely acclaimed as effective adjuvant treatment for primary osteosarcoma.[6-8]

Noting that none of these previous studies included patients who were concomitantly treated by surgery alone, and knowing that a small comparative study at our institution had not found differences between transfer factor and a combination of vincristine, doxorubicin, and methotrexate (MTX) in adjuvant treatment, we decided in 1975 to propose a controlled adjuvant chemotherapy study.[9] By mid-1976 a review had been made of all cases of primary osteosarcoma of bone treated at the Mayo Clinic since 1962 with clear evidence of improvements in both overall survival and postoperative disease-free interval over time unrelated to adjuvant treatment.[10] These results strongly reinforced our interest in a controlled trial, and by late in 1976 institutional Human Studies Committee approval and National Cancer Institute support had been obtained for a prospective randomized comparison between surgery alone versus surgery plus a HDMTX regimen. This study accrued patients slowly for three and one half years until it failed to attract any further cases following a preliminary analysis that did not show an advantage for the group receiving adjuvant chemotherapy.[11] The present report completes our analysis of this pilot study.

MATERIALS AND METHODS

Between November 10, 1976, and May 23, 1980, full discussion of the randomized study was presented to 87 of the 95 medically eligible patients following removal of primary bone sarcomas of their extremities. Two South Americans and one

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Italian patient were residing too far away for close protocol follow-up. One other patient was electively given adjuvant doxorubicin by his personal physician at Mayo Clinic, and in four patients the physician electively or by oversight failed to offer adjuvant study participation.

Eligible patients were judged free of metastatic disease following physical examination, chest roentgenogram, computerized tomography (CT) of the chest, radionuclide bone scan, and bone roentgenograms. All patients had adequate renal, hepatic, and bone marrow function as indicated respectively by serum creatinine <1.2 mg/dL, no increase in direct reacting serum bilirubin, leukocyte count $>4{,}100/\mu L$, and platelet count $>130{,}000/\mu L$. No patient who had previously received cytotoxic drug treatment was accepted. In all patients histologic proof of diagnosis had been obtained prior to total surgical excision of their primary tumors. Forty-one (24 male and 17 female) patients agreed to be included in the randomized study with median age of 17 years (range, 9–62 years). Thirty-eight patients had osteosarcoma, two had fibrosarcoma, and one had rare pleomorphic liposarcoma of bone. No parosteal or other grade 1 tumors were included in the study. Except for four grade 2 osteosarcomas, five grade 3 osteosarcomas, and one grade 3 fibrosarcoma all of the tumors were histologically grade 4. Fifteen tumors arose from the femora, 12 from the tibiae, six from the humeri, four from innominate bones of the pelvis, and one each respectively from the scapula, ulna, radius, and fibula. Surgical excision involved amputation (generally transcortical) except for limb sparing procedures in one patient with osteosarcoma and one with fibrosarcoma.

The osteosarcoma cases were stratified by site of primary disease, histologic grade, predominant histologic pattern, and sex. During the initial postoperative month all patients were assigned according to a dynamic allocation scheme[12] to receive either postsurgical follow-up alone (every six weeks during year one and every three months during year two) or this same follow-up plus a HDMTX regimen (based on Jaffe et al[4]) every three weeks during the initial postoperative year. Vincristine was given intravenously (IV) in doses of 2 mg/m^2 (maximum individual dose, 2 mg) followed one half hour later by a six-hour IV infusion of MTX in 500 mL of 5% dextrose in water. MTX was given in initial doses of 3 g/m^2 of body surface area, with increases to 6 and 7.5 g/m^2, respectively for the second and third doses. For successive treatments the doses were maintained at this level if tolerated and could be further increased by 10% if the drug had been excreted rapidly enough during the preceding dose for the plasma level to reach 1×10^{-7} mol/L within five days. Continuous IV fluids followed the MTX infusion (2,500 mL of 0.45% saline/m^2 daily with 25 mEq KCL and 50 mEq Na HCO_3 added per liter of fluid) with urinary pH of ≥ 7.5 being maintained throughout the infusion. Beginning two hours after completion of the MTX infusion, calcium leucovorin was injected IV in doses of 15 mg every three hours for eight doses, then every six hours until the MTX plasma level was down to $\leq 10^{-7}$ mol/L.

When disease progressed, total excision of the new lesion(s) was accomplished if possible and different therapy was given. Cyclophosphamide (1,200 mg/m^2) was administered IV alternately every three weeks for one year with doxorobucin (75 mg/m^2) to those patients whose metastic sarcoma had been excised during the scheduled MTX treatment or within one year after completing it (maximal total doxorubicin dose, 540 mg/m^2); while those patients who had initially received follow-up alone were given at random either this same alternating regimen or the HDMTX regimen for one year if excision of metastases was possible.

RESULTS

By random selection 20 patients received adjuvant chemotherapy following primary surgery and 21 did not. By chance the three atypical patients (two fibrosarcoma, one pleomorphic liposarcoma) all fell into the control group. These three patients were excluded from our primary analysis. Stratification factors and other variables are presented by treatment groupings for the 38 osteosarcoma patients (Table 1). The two treatment groups appeared to have been reasonably well balanced by these variables. Three of the four osteosarcoma patients with grade 2 tumors were in the control group. Among the six variables listed, only tumor grade and tumor size proved to be prognostically significant for recurrence in proportional hazards models.[13] With median follow-up of approximately five years after study entry (range, 31–74 months), one sided Gehan-Wilcoxon tests of equality of distribution[14] revealed no significant differences in disease-free interval ($p = 0.40$) or survival ($p =$

Table 1. Postsurgical Adjuvant Treatment of Primary Osteosarcoma: Summary of Patient Characteristics

Characteristic	Chemotherapy ($N = 20$)	No Chemotherapy ($N = 18$)*
Age		
≥21 years	7	9
<21 years	13	9
Sex		
Male	14	10
Female	6	8
Histology		
Osteoblastic + telangiectatic	11	10
Chondroblastic + fibroblastic	9	8
Tumor grade		
2 or 3	5	4
4	15	14
Greatest tumor diameter		
≤9 cm	9	9
>9 cm	11	9
Extremity site		
Proximal to knee or elbow	10	9
Distal to knee or elbow	8	6
Limb girdle	2	3

*The three nonosteosarcomas are excluded.

0.26) between those patients who did receive the primary adjuvant HDMTX and those who did not (Figs. 1 and 2). Further analyses including the three atypical control cases produced results almost identical to those above. The treatment variable was still not significant after adjustment for the other covariables. It should be noted that power to detect differences between the two treatment groups was low and estimates of survival and disease-free interval in these small groups were not precise. For instance, the width of the 90% confidence interval of the estimated probability of being disease free at two years (unadjusted for multiple testing) was approximately 0.4 for each group. Thus, the results of this study could be consistent with substantial differences in favor of either treatment group.

Generally the HDMTX regimen was quite tolerable with median lowest leukocyte and platelet nadirs respectively at 3,850/μL (range, 2,800–6,800/μL) and 176,000/μL (range, 34,000–410,000/μL). While some degree of nausea and vomiting was common this was severe in only

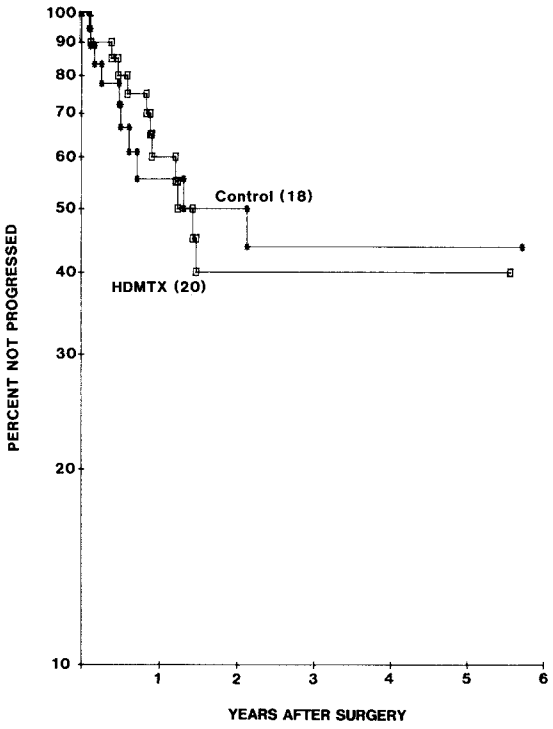

Fig. 1. Estimated probabilities of disease progression following surgery for primary osteosarcoma of bone for 20 patients who received adjuvant HDMTX and for 18 who did not (Kaplan-Meier method)[16] with median follow-up of five years after surgery.

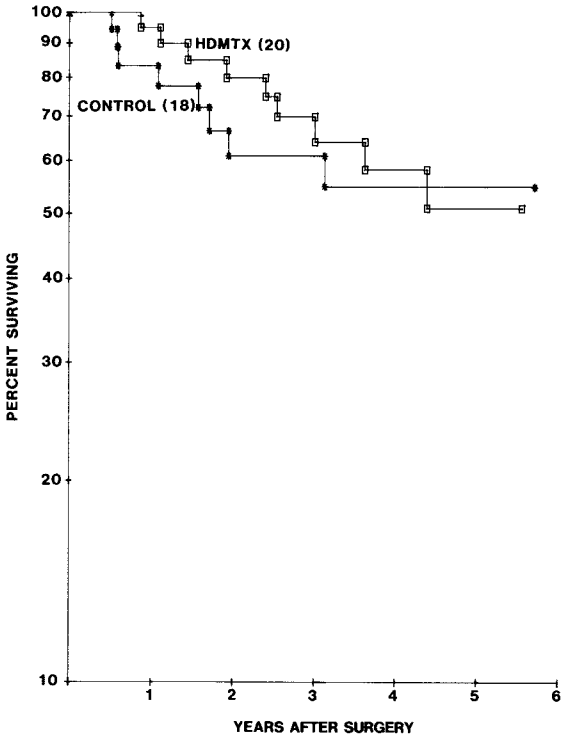

Fig. 2. Estimated probabilities of survival following surgery for primary osteosarcoma of bone for 20 patients who received adjuvant HDMTX and for 18 who did not (Kaplan-Meier method) with median follow-up of five years after surgery.

two cases. Moderate degrees of stomatitis and diarrhea were noted in one and two patients, respectively. One patient developed transient cortical blindness at the 7.5 g/m^2 dose. No serious renal insufficiency was observed; however, delayed drug excretion limited the size of MTX doses in five patients (four at maximal individual doses of 6 g/m^2 and one at 3 g/m^2). Two other patients stopped dosage escalation at maximal doses of 6 g/m^2 because of disease progression.

During follow-up 11 of the 12 patients with osteosarcoma who had disease progression despite primary adjuvant HDMTX treatment have received a total of 29 additional tumor excision operations (primarily thoracotomies) while eight of 10 control patients with disease progression had 19 such operations. Initial disease recurrence has been pulmonary metastasis or pulmonary plus bony metastases except for one control patient whose initial recurrence was in his forequarter amputation stump. Eight of the HDMTX-treated patients were rendered disease free by thoracotomy after initial disease recurrence and

seven accepted treatment with the alternating cyclophosphamide-doxorubicin regimen. The other four were ineligible for protocol crossover because of advanced disease. Among control patients five patients were eligible to be rerandomized and four accepted (two received the HDMTX regimen and two the cyclophosphamide-doxorubicin regimen). Four control patients had advanced disease at the time of first recurrence, and one other control patient was ineligible for secondary chemotherapy because his pulmonary recurrence was excised more than two years after amputation. While all of the nine deaths in the adjuvant treatment group have been disease related, one of the eight control group deaths was suicide in the absence of any postsurgical progression of disease 19 months after entering the study.

We have also analyzed the postmetastasis survival of those patients who have experienced disease progression during follow-up respectively with and without primary adjuvant chemotherapy (Fig. 3). Although theoretically the different secondary treatments given to these two groups of patients could have affected postmetastasis survival, at a median of four years following disease progression no significant differences were found (one sided Gehan-Wilcoxon, $p = 0.22$). Among these 22 osteosarcoma patients who have relapsed despite primary tumor excision with or without the HDMTX regimen, four or five appear to have been salvaged for long-term survival. One of the six survivors in this category has advanced disease and a second has a new single pulmonary nodule by roentgenographic examination.

Finally we have reviewed the survival of the 54 patients (50 with osteosarcoma, one chondrosarcoma, two fibrosarcomas, and one angiosarcoma) who were eligible for our randomized study, but who did not participate. Reasons for not participating (among the 46 offered participation) were varied, including the following: anxiety about toxic effects of chemotherapy, anxiety about not receiving adjuvant treatment, lack of enthusiasm because the investigator could promise no certain value in participation, strong desire to avoid extensive long-distance travel, and simple statement of refusal. In addi-

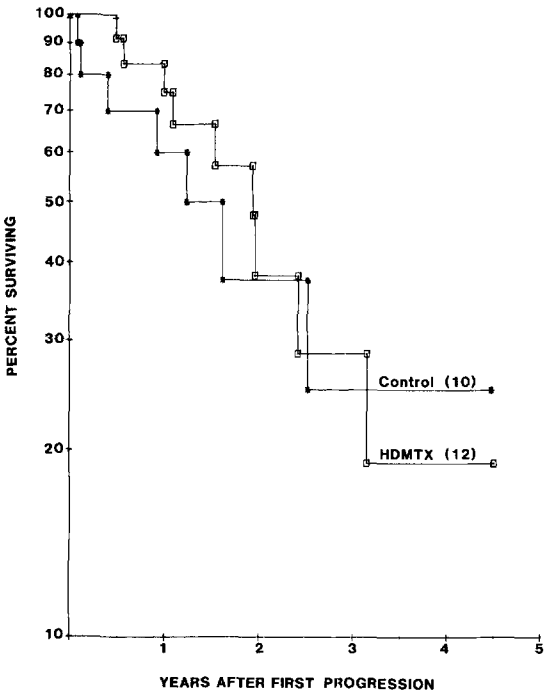

Fig. 3. Estimated probabilities of survival following first progression of disease in 12 patients whose osteosarcomas progressed despite adjuvant HDMTX treatment and in 10 patients whose disease progressed on follow-up alone (Kaplan-Meier method) with median follow-up of four years after disease progression.

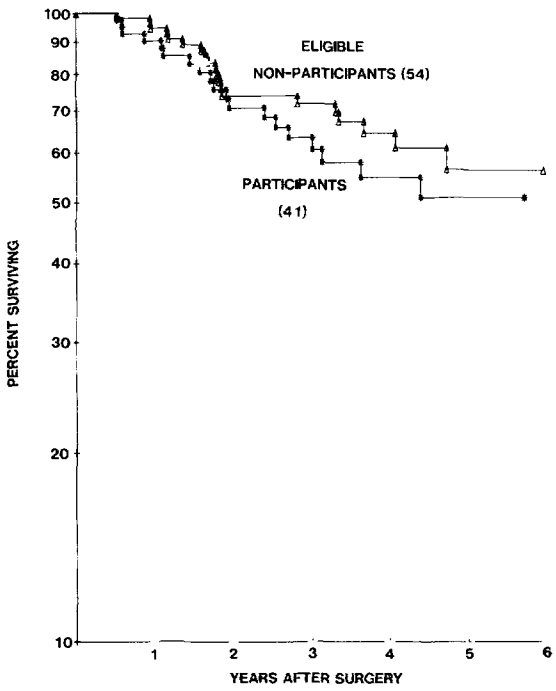

Fig. 4. Estimated probabilities of survival following surgery for all eligible nonparticipants and for all study participants (Kaplan-Meier method).

tion a number of patients delayed any decision statement until the one month postoperative deadline for joining the study had expired. Survival for these 54 patients has been quite similar to that of the 41 patients who participated in our study (Fig. 4). While the majority of the nonparticipants were followed without any additional treatment in the postoperative period, 10 did receive adjuvant chemotherapy including the one treated at Mayo Clinic.

DISCUSSION

With estimated survival of 52% five years after surgery these 38 osteosarcoma patients have exceeded all reasonable survival expectations based on historical reports. Similarly their estimated continuous disease-free status of 42% at five years is truly remarkable when viewed in historical perspective. These figures for both survival and disease-free status, furthermore, are not unlike those from a number of other institutions where similar outcomes have been attributed to the therapeutic effects of adjuvant chemotherapy.[3] A number of recognized and possibly some unrecognized factors might have been involved in this recent unexpected change in overall therapeutic results; however, the better outcome for our patients with primary osteosarcoma cannot be attributed primarily to adjuvant chemotherapy.

Our present study results do not support the thesis that adjuvant treatment with HDMTX has been a significant factor in the generally recognized recent improvement in disease outcome for patients with primary osteosarcoma. Because of the limited scope and multiple analyses of our pilot study, however, these results do not prove that HDMTX has no favorable effects in this role. In fact, our results could be consistent with substantial favorable (or unfavorable) effects. Perhaps other antisarcoma agents or combinations might be superior to HDMTX as adjuvant treatments and perhaps even higher doses of MTX might be more active. Larger controlled studies of adjuvant chemotherapy in primary osteosarcoma are needed. Our pilot study has confirmed the continued need for concomitant untreated control patients in determining the value of adjuvant chemotherapy programs for patients with primary osteosarcoma, and we support current efforts of the members of the Pediatric Oncology Group to perform a randomized multiinstitutional comparison between surgery alone and surgery plus the cytotoxic drug regimen reported in phase II trials to have yielded the best results to date.[15]

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