นิพนธ์ต้นฉบับ

Adjuvant chemotherapy for non-metastatic osteosarcoma of the extremity : a preliminary report.

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Nine cases seven males and two females of non-metastatic osteosarcoma of the extremity were treated with chemotherapy in an adjuvant fashion. The primary lesion was in the distal femur in five patients, the proximal tibia in two, and one each in the distal tibia and proximal femur. Pre-operative chemotherapy with intra-arterial cisplatin (100 mg/m^2) and intravenous dexorubicin (60 mg/m^2) was administered in two patients. Post-operatively, cisplatin (100 mg/m^2) and dexorubicin (60 mg/m^2) were given intravenously for one year. Doxorubicin was given until the dose reached a total of 450 mg/m^2. Surgery consisted of limb-sparing surgery in four of the cases, above-knee amputation in three, and one each of hip-disarticulation and below-knee-amputation. Four of the nine patients were disease-free past 24 months. The two-year disease-free survival rate was 50.1% and overall survival was 87.5%. Refinements in treatment and more thorough pre-treatment investigations are discussed.

Key words : *Chemotherapy, radiotherapy, adjuvant, osteosarcoma, extremity*

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รายงานผู้ป่วยมะเร็งกระดูก ชนิด osteosarcoma ที่ยังไม่ได้กระจายไปที่อื่น 9 ราย ซึ่งได้รับการรักษาเสริมด้วยเคมีบำบัด ผู้ชาย 7 ราย ผู้หญิง 2 ราย มะเร็งเป็นที่ distal femur 5 ราย proximal tibia 2 ราย distal tibia และ proximal femur อย่างละ 1 ราย เคมีบำบัดก่อนผ่าตัดประกอบด้วย intra arterial cisplatin (100 mg/m^2) และ doxorubicin (60 mg/m^2) หลังผ่าตัดผู้ป่วยได้รับ cisplatin 100 mg/m^2 และ doxorubicin 60 mg/m^2 เป็นเวลา 1 ปี จำกัดขนาดยา doxorubicin สูงสุดที่450 mg/m^2 ผลการรักษาเป็นที่น่าพอใจ อัตราปลอดโรคในระยะ 2 ปี = 50.1% อัตราการอยู่รอดในระยะ 2 ปี = 87.5% ถึงแม้การกลับเป็นใหม่ตรงตำแหน่งเดิมและการกระจายไปปอด ยังเป็นสาเหตุสำคัญที่ทำให้ผู้ป่วยเสียชีวิต ผลการศึกษาของเรายังสนับสนุนการใช้เคมีบำบัดเพื่อรักษาเสริมในโรคนี้

อย่างไรก็ตาม ผู้รายงานเห็นว่ายังจะต้องมีการปรับปรุงขนาดของยาเคมีที่ให้กับผู้ป่วย การนำรังสี รักษามารักษาร่วม และการใช้เอ็กซเรย์คอมพิวเตอร์มาช่วยตรวจหาระยะของโรค โดยเฉพาะที่ปอด

Major advances in the management of non-metastatic osteosarcoma of the extremity have been made during the past 15 years. Adjuvant chemotherapy has been shown to improve the disease-free survival rate.[1-3] The rationale of pre-operative intra-arterial infusion of chemotherapy is that it facilitates limb-sparing surgery.[4,5] Pulmonary resection of lung metastases has been the practice in many centers and shown to improve survival.[6,7] Prophylactic whole lung irradiation has been carried out by many authors and the results have been encouraging.[8,9]

We are reporting the preliminary results of disease-free and overall survival in treating with adjuvant chemotherapy nine patients who had non-metastatic osteosarcoma of the extremity.

Material and methods.

From January 1986 through December 1989, nine cases of non-metastatic osteosarcoma of the extremity were referred to the Department of Radiology, Faculty of Medicine, Chulalongkorn University for adjuvant chemotherapy. After the diagnosis had been confirmed by biopsy, evaluation for metastases was performed. All patients had a chest x-ray to rule out lung metastases. Radionuclide bone scan was done in cases in whom bone metastases had been suspected. Routine blood tests, including completed blood count, blood urea nitrogen, creatinine, liver function, electrolytes, uric acid, calcium, phosphate and magnesium, were obtained prior to administration of each cycle of chemotherapy. Electrocardiogram and left ventricular ejection fraction study were used to assess cardiac function. Computerized tomography (CT) of the lung was not used routinely to evaluate lung metastases. There were 7 males and 2 females. The primary tumor affected the right extremity in 6 patients and the left in 3 patients. The femur was affected in 6 patients and the tibia in 3 patients. The distal femur was the most common site of the primary, affecting 5 cases. The next sites of the primary tumor were : upper tibia (2 patients), upper femur (1 patient), and lower tibia (1 patient). Our adjuvant chemotherapy program consisted of pre or post-operative administration of cisplatin (Platinol; Bristol-Myers Oncology, New York, New York, U.S.A.) and doxorubicin hydrochloride (Adiblastina; Farmitalia Carlo Erba S.P.A., Montedison Group, Italy). Patients destined for limb-sparing surgery received pre-operative chemotherapy which consisted of intra-arterial infusion of cisplatin and intra-venous doxorubicin. Intravenous doxorubicin was given in dosages of 60 mg/m^2 on the first day, escalating to 75 mg/m^2 on the subsequent courses. Intra-arterial cisplatin was administered in dosages of 100 mg/m^2 on the second day with prior hydration according to the regimen by Jaffe.[10]

It was intended that the total number of courses of pre-operative chemotherapy would be four courses. Patients responding to pre-operative chemotherapy (criteria of response will be defined later) were scheduled to receive the same chemotherapy (cisplatin and doxorubicin intravenously) post-operatively for one year, omitting doxorubicin after the patient had attained 450 mg/m^2. If response to pre-operative chemotherapy was sub-optimal, Ifosfamide (Holoxan; Asta-Werke, Degussa Pharma Grupoe, Germany), in dosages of 50-60 mg/Kg/day intravenously for five days with mesna protection,was given post-operatively for one year. For patients having immediated radical surgery, intravenous doxorubicin 60 mg/m^2 on day 1 and cisplatin 100 mg/m^2 on day 2 with prior hydration were given for on year. The doses of doxorubicin and cisplatin were escalated to 75 mg/m^2 and 120 mg/m^2, respectively, on subsequent courses. After having received a total of 450 mg/m^2 of doxorubicin, it was dropped from the schedule and cisplatin alone was given for the rest of the therapy. Either pre-or post-operative chemotherapy was given every 3-4 weeks (Table 1,2).

Table 1. Pre-operative chemotherapy.

Drugs	Daily dose mg/m^2	Administration route	Administration on day	Frequency
Cisplatin	100	IA	1	Recycle
Doxorubicin	60-75	IV	1	every 4 weeks

Table 2. Post-operative chemotherapy.

Drugs	Daily dose mg/m²	Administration route	Administration on day	Frequency
Cisplatin	100	IV	1	Recycle
Doxorubicin	60-75	IV	1	every 4 weeks

Arterial catheterization for infusion of cisplatin was performed under local anesthesia by the Seldinger technique.[11] The cisplatin was infused intra-arterially for 2-4 hours. Metoclopramide was given intravenously for nausea and vomiting.

Two patatients received CONPADRI-1.[12]

Limb-sparing surgery was performed by local excision of the tumor, with generous margin, and replacement with bone graft or endoprosthesis.

Four patients (No. 3,4,6,8) had limb-sparing surgery. Two (No. 3,8) of these four patients had prior intra-arterial infusion of cisplatin before limb-sparing surgery. Three patients (No. 5,7,9) with distal femur tumor underwent above-knee amputation. There was a single patient (No.1) with distal femur tumor who had hip disarticulation. Below-knee amputation was performed in only one patient (No. 2) with distal tibia tumor.

Prophylactic lung irradiation was given in only one patient (No. 7). She refused further irradiation after attaining a midlung dose of 750 cGy/1 week. Pre-operative irradiation to the primary was administered in one patient (No.9).

Assessment of response to pre-operative chemotherapy was determined by changes in clinical symptoms, percentage of pathological tumor necrosis, or by resolution of tumor vascularity angiographically.[13] Changes in clinical symptoms were evaluated by diminishing pain or regression in tumor size. Angiographic response was determined by the disappearance of tumor vascularity and tumor stain, or a total disappearance of tumor vascularity with slight persistence of capillary stain.[13]Pathological tumor necrosis greater than 90% was considered a good response to intra-arterial chemotherapy.[13]

Relapse was defined as a recurrence of tumor at any site. Local recurrence and distant metastases were defined, respectively, as recurrence of tumor at the primary site and at sites other than the primary one.

Toxicity was measured according to the World Health Organization (WHO) grading system.[14]

The date of therapy initiation was used as the starting time for survival calculation. The study end points were disease-free survival and survival. The Kaplan Meier method was used for calculation of survival.[15]

Results

Between January 1986 and December 1989, 15 patients with osteosarcoma of the extremity were registered for adjuvant chemotherapy. Of these, six were not eligible for the study due to distant metastases at presentation. Nine patients remained who could be studied. The minimal and maximal follow-up times were seven months and 80+ months, respectively, with the median being 33 months.

The clinical data of the patients are shown in Table 3. The age of the patients ranged from 10 to 22 years, with the median age being 18 years. The most frequent presenting symptom duration of 1-6 months, the median being 3 months, and a history of mass or pain.

Of the two patients who had pre-operative intra-arterial infusion, one patient (No. 8) was considered to have "angiographic response" and tumor necrosis of over 90% after four courses of intra-arterial infusion of cisplatin. The other patient (No.3) was operated on after having been given only one course of chemotherapy.

Local recurrence occurred in three patients (33.3%) and these recurrences occurred exclusively in the four patients who had undergone limb-sparing surgery. Pulmonary metastases were observed in five patients (55.6%), one of whom had malignant pleural effusion. One patient (No.8) had both local and distant relapses.

At the time of data analysis (January 1993), six patients had died, three were alive : one with pulmonary metastases and two without disease. The two -year disease free-survival rate was 50.1%; overall survival was 87.5%.

Toxicity was mild. All patients had grade 1 hemato-toxicity and grade 3 alopecia.

Table 3. Clinical data of the nine patients treated with adjuvant chemotherapy.

Patient number	Age/Sex Year/Male or Female	Symptoms mass/pain (months)	Primary tumor site	Treatment modality	Surgery	Total dose doxornbicin (mg.)	Total dose cisplatin (mg.)	NED (months))	OS (months)	Current status	Comments
1.	10/M	5	Left distal femur	S/C	Hip disar-ticulation	220	-	80+	80+	A/W	Received CONPADRI-1.[24]
2.	21/M	6	Right distal tibia	S/C	BKA	440	-	22	33	Dead	Received CONPADRI-1[24] Pulmonary metastasis 22 months following treatment.
3.	18/M	1	Right proximal tibia	A/S/C	L-S	600	600	14	30	Dead	Pulmonary metatasis 14 months following treatment.
4.	22/M	3	Right proximal tibia	S/C	L-S	550	850	7	7	Dead	He was a foreigner who was lost to follow-up after a local recurrence at 7 months (Assumed to have died.)
5.	18/M	3	Right distal femur	S/C	AKA	440	900	13	15	Dead	Pulmonary metastasis 15 months following treatment.
6.	16/F	5	Left proximal femur	S/C	L-S	960*	1300	29	33	Dead	Local recurrence 29 months following treatment. She died from DVT.
7.	19/F	3	Left distal femur	S/C	AKA	300	600	52+	52+	A/W	Refused further chemotherapy. Received whole lung irradiation 750 cGy/1 wk.
8.	11/M	4	Right distal femur	A/S/C	L-S	630	650	30	45+	A/M	Local recurrence at 30 months and pulmonary metastasis at 34 months following treatment. 90+% tumor necrosis after IA CDDP.
9.	10/M	1	Right distal femur	R/S/C	AKA	550	770	24	28	Dead	Radiation therapy pre-operatively of the primary (800 cGyx2 fractions) Malignant pleural effnsion 24 months following treatments.

S = surgery; C= chemotherapy; a= intra-arterial chemotherapy; R= radiation therapy; A/W = alive and well; BKA = below knee-amputation;
L-S = limb sparing surgery; AKA= above-knee amputation; DVT= deep vein thrombosis; A/M= alive with metastasis; CDDP= cisplatin
NED = no evidence of disease; OS= overall survival.
* Epirulicin.

Discussion

Cade,[16] in 1955, reported a method of irradiation followed by delayed amputation if no pulmonary metastases had developed at six months. The method yielded a two-year survival rate of 20%.

Douglass and co-workers from Roswell Park Memorial Institute[17] reported, in 1975, a 12% five-year survival rate in patients with osteosarcoma treated with amputation alone. Between 1966 and 1972, other authors also reported a cure rate of 15-20%.[18-20]

In the past several years major advances in incorporating adjuvant chemotherapy in the management of non-metastatic osteosarcoma of the extremity produced a two-year disease free- survival rate in excess of 50%.[1-3] The most widely used chemotherapeutic agents are cisplatin, doxorubicin and high-dose methotrexate.

This study was undertaken to evaluate the effect of adjuvant chemotherapy on disease-free survival and overall survival. The two-year disease-free survival rate of our patients was 50.1%, overall survival was 87.5%. These results compare favorably with those of other reports[1-3] and are better than that of our patient who underwent surgical treatment alone (2-year disease-free survival = 11.1%, overall survival = 22.2%).[21] Before the widespread use of chemotherapy, the incidence of pulmonary metastases was at least 80%. This figure has dropped to 30-40% with the advent of adjuvant chemotherapy. Guiliano et al.[22] reported an incidence of 47%. In this report the incidence of pulmonary metastases was 55.6%. This high incidence of pulmonary metastases, despite administration of adjuvant chemotherapy, could be due to two factors. Firstly, pre-treatment evaluation of our patients did not include CT scan of the chest to rule out pulmonary metastases at presentation. The sensitivity of a standard chest x-ray was only 57%.[23] Secondly, most of the patients received suboptimal doses of chemotherapy. Drug dose instensity has been reported to be an important determinant of prognosis.[24,25]

Local recurrence was also a major cause of failure. It is interesting to note that all the local recurrences occurred in patients who had limb-sparing surgery. Although an attractive procedure sparing the young patient an amputation, limb-sparing surgery has still to be refined, possibly by incorporating radiation of the primary tumor prior to surgery in order to reduce local recurrence.

Conclusion

Our experience in treating with adjuvant chemotherapy a small number of patients having osteosarcoma of the extremity compares favorably with that of other reports in the literature.[1-3] We achieved a two year disease-free survival rate of 50.1% and overall survival of 87.5%. Although pulmonary metastases and local recurrence are still the major causes of failure, our results support the use of adjuvant chemotherapy for patients presenting with non-metastatic osteoarcoma of the extremity. Long-term results are awaited. Refinements in treatment have to be made in order to reduce the aforementioned types of failure. In our subsequent trial, pre-operative staging with CT scan of the lung, optimal dosages of chemotherapy and prophylactic lung irradiation will be incorporated in our treatment program.

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References

1. Link MP, Goorin AM, Miser AW, Geen AA, Pratt CB, Belasco JB, Pritchard J, Malpas JS, Baker JJ, Kirkpatrick JA. The effect of adjuvant chemotherapy on relapse-free survival in patients with osteosarcoma of the extremity. N Engl J Med 1986 Jun; 314(25) : 1600-6
2. Eilber F, Giuliano A, Eckardt J, Patterson K, Moseley S, GoodnightJ.Adjuvant chemotherapy for osteosarcoma : A randomized prospective trial. J Clin Oncol 1987 Jan; 5(1) : 21-6
3. Goorin AM, Shuster JJ, Baker A, Horowitz ME, Meyer WH, Link MP. Changing pattern of pulmonary metastases with adjuvant chemotherapy in patients with osteosarcoma : Results from the Multi-Institutional Osteosarcoma Study. J Clin Oncol 199 Apr; 9(4) : 600-5
4. Jaffe N, Prudich J, Knapp J, Wang YM, Bowman R, Caugir A, Ayala A, Chuang V. Treatment of primary osteosarcoma with intra-arterial and intravenous high-dose methotrexate. J Clin Oncol 1983 Jan; 1(1) : 428-31
5. Stine KC, Hockenberry MJ, Harrelson J, Miner D, Falletta JM. Systemic doxorubicin and intra-arterial cisplatin preoperative chemotherapy plus postoperative adjuvant chemotherapy in patients with osteosarcoma. Cancer 1989 Mar; 63(5) : 848-53
6. Meyer WH, Schell MJ, Kumar APM, Kumar M, Rao BN, Green AA, Champion J. Thoracotomy for pulmonary metastatic osteosar-

coma An analysis of prognostic indicators of survival. Cancer 1987 Jan; 59(2) : 374-9
7. Belli L, Scholl S, Livartowski A, Ashby M, Palangie T, Levasseur P, Pouillart P. Resection of pulmonary metastases in osteosarcoma : A retrospective analysis of 44 patients. Cancer 1989 Jun; 63(12) : 2546-50
8. Rab GT, Lvins JC, Childs DS, Cupps RE, Pritchard DJ. Elective whole lung irradiation in the treatment of osteogenic sarcoma. Cancer 1976 Aug; 38(2) : 939-42
9. Burgers JMV, Glabbeke M, Busson A, Cohen P, Mazabraud AR, Abbatucci JS, Kalifa C, Tubiana M, Lemerle JS. Osteosarcoma of thelimbs:Report of the EORTC-SIOP 03 trial 20781 investigating the value of adjuvant treatment with chemotherapy and/or prophylactic lung irradiation. Cancer 1988 Mar; 61(5) : 1024-31
10. Jaffe N, Knapp J, Chuang VP, Wallace S, Ayala A, Murray J, Cangir A, Wang A. Osteosarcoma. Intra-arterial treatment of the primary tumor with cis-diammine-dichloroplatinum II (CDP). Cancer 1983 Feb; 51(3) : 402-7
11. Seldinger SI. Catheter replacement of the needle in percutaeous arteriography. Acta Radiologica 1953 May; 39(5) : 368-76
12. Sutow WW, Gehan EA, Vietti TJ, Frias AE, Dyment PG. Multidrug chemotherapy in primary treatment of osteosarcoma. J Bone Joint Surg 1976 Jul; 58A(5) : 629-35
13. Carrasco CH, Charnsangavej C, Raymond AK, Richli WR, Wallace S, Chawla SP, Ayala AG, Murray JA. Osteosarcoma : Angiographic Assessment of response to preoperative chemotherapy Radiology 1989 Mar; 170(3) : 839-42
14. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer 1981 Jan; 47(1) : 207-14
15. Buyse ME, Staquet MJ, Sylvester RJ. Cancer Clinical Trials : Methods and Practice. Oxford University Press, 1984 : 342-5
16. Cade J Osteogenic sarcoma : a study based on 133 patients. J R Cool Surg Edinb 1955; 1 : 79-111
17. Douglass HO Jr, Wang J, Takita H, Wallace HJ, Friedman M, Mindell E. Improvement in the results of treatment of osteogenic sarcoma. Surg Gynecol Obstet 1975 May; 140(5) : 693-700
18. Dahlin DC, Voventry MB. Osteogenic sarcoma : A study of six hundred cases. J Bone Joint Surg 1967 Jan; 49 A(1) : 101-10
19. Marcove RC, Mike v, Hajek JV, Levin AG, Hutter RVP. Osteogenic sarcoma in childhood. NY State J Med 1971 Apr; 71(8) : 855-9
20. Friedman MA, Carter SK. The therapy of osteogenic sarcoma : current status and thoughts for the future. J Surg Oncol 1972; 4(5/6) : 482-510
21. Rojpornpradit P. Unpublished data.
22. Giuliano AE, Feig S, Eilber F, Changing metastatic patterns of osteosarcoma. Cancer 1984 Nov; 54(10) : 2160-4
23. Vanel D, Henry-Amar M, Lumbroso J, Lamelet E, Couanet D, Piekarski JD, Masselot J, Boddaert A. Pulmonary evalutation of patients with osteosarcoma : Roles of standard radiography, tomography, CT, scintigraphy, and tomoscintigraphy. AJR 1984 Sep; 143(3) : 519-23
24. Prasad R, Bacci G, Campanacci M, Picci P. Does drug dose intensity of chemotherapy detemine the prognosis of primary high grade osteosarcoma. Proc ASCO 1990 Mar; 9(1202) : 311
25. Delepine N, Delepine G, Desbois JC, Prognostic value of durg intensity and seric intensity of MTX in osteosarcoma. Proc ASCO 1992 Mar; 11(1465) : 417