

Efficacy of Pre- and Postoperative Chemotherapy in Patients with Osteosarcoma of the Extremities

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Purpose: We evaluated the treatment efficacy including survival and recurrence, and factors associated with recurrence in osteosarcoma patients treated with preoperative chemotherapy, surgery, and adjuvant chemotherapy.

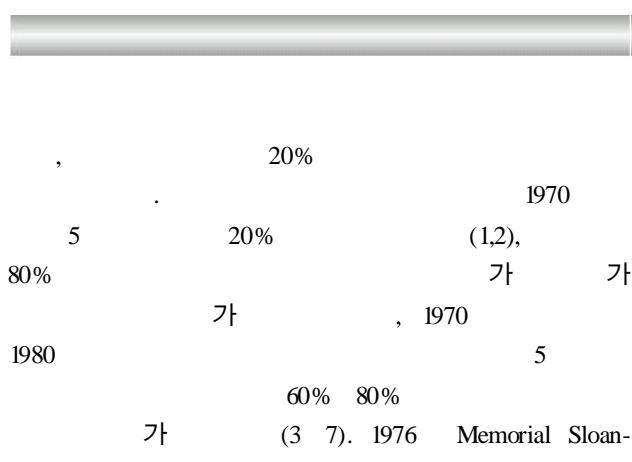
Materials and Methods: Forty nine patients with osteosarcoma were treated with preoperative chemotherapy with intra-arterial cisplatin and adriamycin infusion for 3 cycles, followed by surgery. According to the pathologic response, if tumor was necrotized more than 90%, the same adjuvant chemotherapy was reintroduced for 3 cycles, and if the response was not enough, then the salvage regimen was introduced. Plain chest film and chest CT scan were taken monthly and every 3 months, respectively. When tumor recurred, the metastasectomy was performed whenever possible.

Results: Forty three patients were evaluable with a

median follow up of 53 months. Five-year disease-free and overall survival rate was 47.0% and 66.9%, respectively. The recurrence was observed in 22 patients (51.2%) with median time of 12.5 months. Baseline alkaline phosphatase (ALP) was the only significant factor for recurrence ($p=0.03$) and the patients with the possibility of metastasectomy recurrence showed higher post-relapse survival compared to other treatment modalities (26 months vs 5 12 months).

Conclusion: These results indicates that pre- and postoperative chemotherapy with intra-arterial cisplatin and adriamycin infusion showed comparable treatment efficacy and acceptable toxicities. (*Cancer Research and Treatment 2001;33:520-526*)

Key Words: Osteosarcoma, Neoadjuvant chemotherapy, Recurrence, Metastasectomy



Kettering Cancer Center (MSKCC) Rosen
 methotrexate (HDMTX) 가
 (T10 regimen) 5
 가 , 가
 (4,7). , HDMTX, adriamycin, cisplatin, ifosfamide
 , ,
 cisplatin adriamycin 37 ,
 3 , 54.7%,
 78.3% ,
 (8). 1990 1
 1997 12 43
 5 ,

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(ifosphamide 60%
가 500
(G-CSF)

1)
1990 1 1997 12
49
IIB
ray
Enneking (9).
2)
, cisplatin 120 mg/m² 2
24 2 4 adriamycin 25 mg/m²/day
(AP).
3 3 cycle
3 . , 1 2
3
2 4 , Rosen
가 (7), 90%
(Grade III, IV)
cycle . 90%
(Grade I, II)
IMVP-16 , 1 methotrexate 10 g/m²,
1 5 ifosfamide 1.5 g/m²/day, 1 3
etoposide 120 mg/m²/day
3 6 cycle (Fig. 1). metho-
trexate leucovorin rescue ifosfa-
mide mesna

3)
(CBC), alkaline phosphatase
(ALP)
3
가 가
가 90% IMVP-16
6
가 IMVP-16
가 가
가 가
4)
(Dose intensity, DI)
(mg/m²/
(Relative dose intensity, RDI)
가
. 43
22
가
(progression free survival)
(overall survival)
Kaplan-
Meier log-rank test
analysis) logistic regression
(univariate
analysis)

1)
49 4 2 3
2

43 가 . 가가 가
 43 22 , 21 16
 (: 8 41) .
 20 (46.5%), 10 (23.3%), 8 (18.6%),
 2 (4.7%), 1 (2.4%),
 1 (2.4%), 1 (2.4%) . osteo-
 blastic type 22 (51.2%), chondroblastic type 4 (9.3%), mixed
 type 4 (9.3%), fibroblastic type 2 (4.7%), telangiectatic type
 1 (2.3%) 가 가 10 (23.3%)
 . 10 cm 29 (67.4%), 10
 cm 14 (33.6%) . ECOG
 0 1 28 (65.1%), 2가 15 (34.9%) (Table 1).
 2)
 3 cycle (1 5) ,
 adriamycin 0.89, cisplatin 0.93 .
 0.76 .
 33 (76.7%)
 10 (23.3%) . 43 81.4%
 35 .
 , 16/21 , 17/22
 , 가 .
 , WHO
 grade IV 29 (67.4%)
 16 (37.2%) . WHO grade IV
 1 (2.3%), 3 (7.0%) . AP
 IMVP-16 , WHO grade
 III, IV AP ,
 , ,
 2 ,
 . 3 AP
 ,
 AP
 . IMVP-16
 1 amino-
 glycoside ,
 , 가
 .
 3)
 53 (

Table 1. Patients characteristics

Number of total patients	49
Number of evaluable patients	43
Age (median)	8 41 (16)
Sex (M : F)	22 : 21
Performance status (%)	
0 1	28 (65.1)
2	15 (34.9)
Site (%)	
Distal femur	20 (46.5)
Proximal tibia	10 (23.3)
Humerus	8 (18.6)
Proximal femur	2 (4.7)
Others	3 (7.0)
Size (%)	
< 10 cm	29 (67.4)
10 cm	14 (33.6)
Pathologic type (%)	
Osteoblastic	22 (51.2)
Chondroblastic	4 (9.3)
Mixed	4 (9.3)
Fibroblastic	2 (4.7)
Telangiectatic	1 (2.3)
Unknown	10 (23.3)
Alkaline phosphatase	
Mean ±SD (IU/L)	281±209
No of patients (%)	
< 300	28 (65.1)
300	15 (34.9)
Median cycle of treatment (range)	
Neoadjuvant	3 (1 5)
Adjuvant	3 (1 9)
Median AP* RDI† (range)	
Neoadjuvant	0.90 (0.44 1.00)
Adjuvant	0.76 (0.51 1.00)
Median dose density (range)	94% (58 110)
Operation (%)	
Amputation	8 (18.6)
Limb-salvage	35 (81.4)

*Adriamycin, Cisplatin, † Relative Dose Intensity

30 119), 5 47.0%,
 5 66.9% (Fig. 1).
 58 (95% CI 24 92)
 74 (95% CI 62 86) . 5
 51%, 5 71% ,
 5 30%, 5 45% .
 74 (95% CI 64 84)

Table 2. Predictive factors for relapse

Variable	Discrimination	Univariate analysis p-value	Odds ratio	Multivariate analysis p-value
Histologic response	NR*/R [†]	0.037	7.85	0.051
Alkaline phosphatase	< 300/ 300	0.033	9.20	0.030
Surgery type	amputation/limb-salvage	0.391		
Sex	male/female	0.650		
Age	< 20/ 20	0.933		
Size	< 10 cm/ 10 cm	0.065	3.09	0.161
Site	distal/proximal	0.337		
Dose intensity				
Adjuvant	below/above median	0.288	0.27	0.156
Neoadjuvant	below/above median	0.287	0.41	0.317

*Nonresponder, [†] Responder

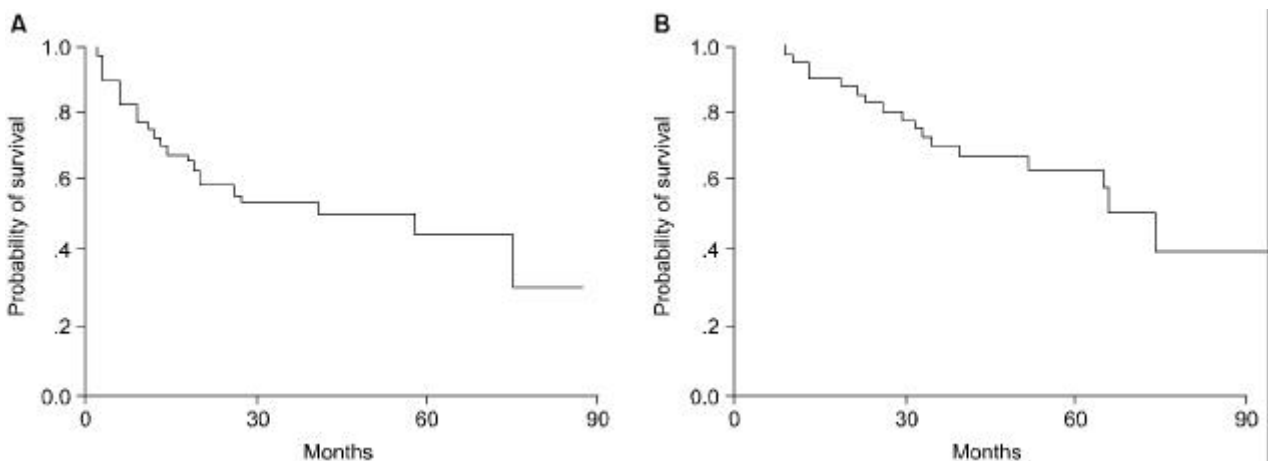


Fig. 1. Survival curves of all osteosarcoma patients (n=43) with median follow up of 53 months (range 30 – 119) A: Disease free survival, B: Overall survival

52 (95% CI 13 – 91)
 (p=0.71).
 22 (51.2%)
 12.5 . 33 14 가
 10 8 가 . 가
 (20 , 90.9%) 가 1
 (3.7%). 5 (22.7%), 4
 가 (Fig. 2).
 22 10
 26 ,
 3
 5 . 9 salvage 2

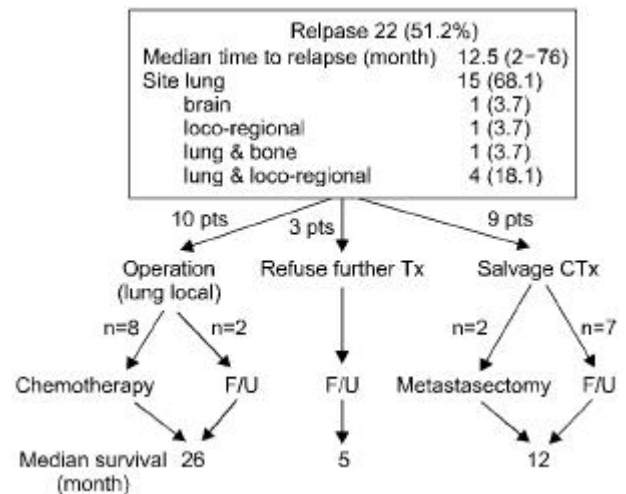


Fig. 2. Patterns of failure & treatment

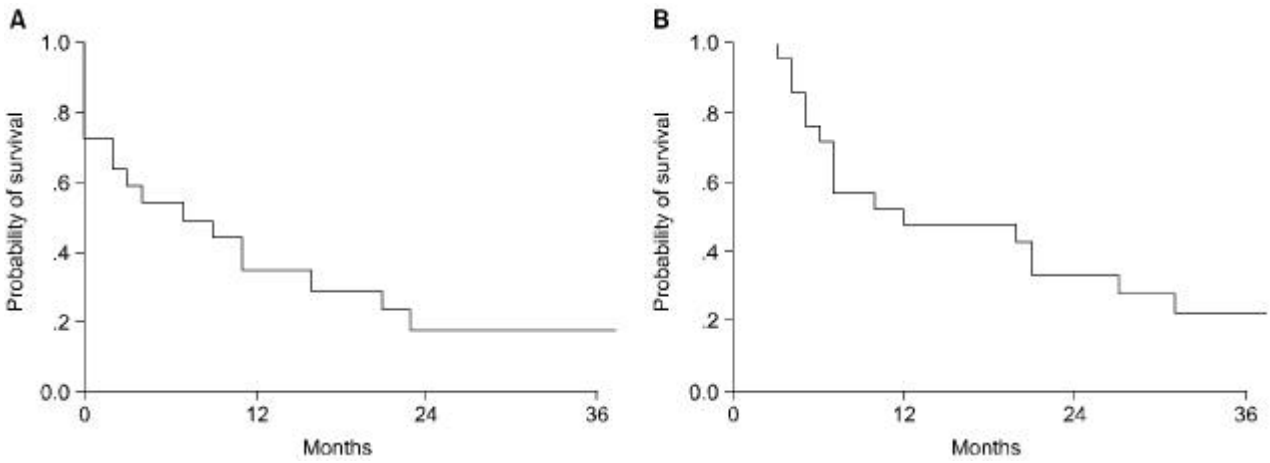


Fig. 3. Survival curves of all relapsed osteosarcoma patients (n=22) with median follow up of 53 months (range 3-85) A: Progression-free survival, B: Overall survival

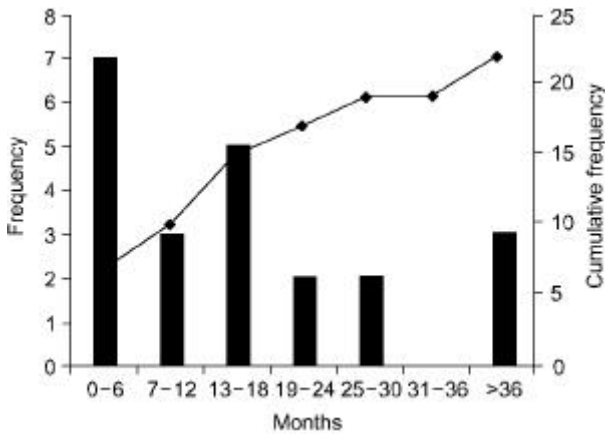


Fig. 4. Frequency of recurrence analyzed by time interval after operation

12 (Fig. 3).
 38 (3 85) ,
 9 (0 66)
 12 (3 66) (Fig. 3).

4)

0 12 10 (45.4%), 12 24
 7 (31.8%) 24 48 3 (13.6%), 48
 2 (9.1%) (Fig. 4).

, logistic regression
 , borderline significance
 (p=0.051), ALP

(p=0.03)(Table 2).

(:
 26 vs 5 12).



1976 Rosen

가

, (salvage chemotherapy)
 , 가 .
 , 60%
 80% , 가

(5,11 15).

, Rosen T10 (HDMTX, adriamycin, bleomycin, cyclophosphamide, dactinomycin)

가

가

adriamycin, HDMTX, cisplatin, ifosfamide

, 가
 (13 16,18,19).

1983 Jaffe

가

, 2

가 , (20,21), 5 23 50%
 , 4 0%
 cisplatin (13,22).
 adriamycin , 3 (23). , MTX(16)
 60%, 40% (p=0.21), 67% ifosfamide
 85%, 78% (p=0.52) (8). (24) etoposide 가
 , 가 , (17). etoposide ifosfamide etoposide
 , 가 , Bacci ifosfamide etoposide
 가 ,
 (12). , 가
 , (metastasectomy) ifosfamide, etoposide HDMTX,
 AP IMVP-16
 (12).
 22 , 10
 , 9
 , 2
 가
 ,
 (26, 12, 5).
 , cisplatin adriamycin
 24 5 5
 2 (51.2%) , 2
 X-ray 가 ALP
 (metastasectomy)
 가 , Rosen
 , (10,14,15). MTX
 가 가 (15).
 , ALP
 borderline significance
 가 ,
 가 가

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