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Case Report

Histological assessment of the effect of neoadjuvant chemotherapy on conventional high grade osteosarcoma of the long bones

Thapa JB[1]

[1]*Department of Pathology, Himal Hospital Pvt. Ltd., Kathmandu, Nepal*

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ABSTRACT

A multidisciplinary team of an orthopaedic surgeon, medical oncologist, radiologist and pathologist was involved in the management of osteosarcoma cases. Four cases of osteosarcoma were examined for the effects of neoadjuvant chemotherapy. Total histological mapping was done to study the post-chemotherapy biopsies. Two cases were good responders (more than 90% response), and two cases were poor responders (less than 90% response). Good responders had limb sparing surgery performed on them. Long term follow up results are awaited.

INTRODUCTION

Osteosarcoma often presents as a high grade aggressive bony neoplasm affecting mostly the young and sometimes the elderly. Adoption of a robust multi-specialty and multimodality therapeutic strategy worldwide has made significant strides in the management of this neoplasm. Though most of the medical manpower are often scattered working in the different institutions in Kathmandu, we too have started to use a team of an orthopedic surgeon, medical oncologist, radiologist and pathologist for the diagnosis and management of the tumour using neoadjuvant chemotherapy followed by surgery, often limb sparing. This study was done to study the effect of chemotherapy on the tumour mass.

CASE SERIES

Four osteosarcoma cases were referred in the last year from Capital Hospital for pre and post neoadjuvant chemotherapy tumour response histological study. Biopsy specimens along with the relevant clinical information and imaging films were used. The subjects were biopsy confirmed osteosarcoma patients who were to undergo neoadjuvant chemotherapy at Capital Hospital. Patients were committed to long term care and follow up at that hospital. Two biopsies were used in each case to study the response of the sarcoma to the chemotherapy. The first biopsy was initially done as a diagnostic biopsy, and consisted of either an incisional biopsy or wide bore needle biopsy. This was followed by a set of chemotherapy administered before to the surgery. A second biopsy was then done with wide excision of the bone involved. This was subjected to total histological mapping in the laboratory to study the effect of chemotherapy on the tumour cells as per Huvos et al – Memorial Sloan-Kettering Cancer Center,[1] Salzer-Kuntschik et al – German-Austrian-Swiss Cooperative Osteosarcoma Study Group (COSS),[2] Picci et al[2] – Instituti Ortopedico Rizzoli (IOR) in Bologna. (fig. 1)[3] In this study the more widely accepted criteria i.e. more 90% necrosis as a good responder and <90% necrosis as a poor responder was used to separate the good responders from the poor responders (fig. 2).

Correspondence:
Dr. Jung B. Thapa
Department of Pathology, Himal Hospital Pvt. Ltd., Kathmandu, Nepal
Email: jungbahadurthapa@gmail.com

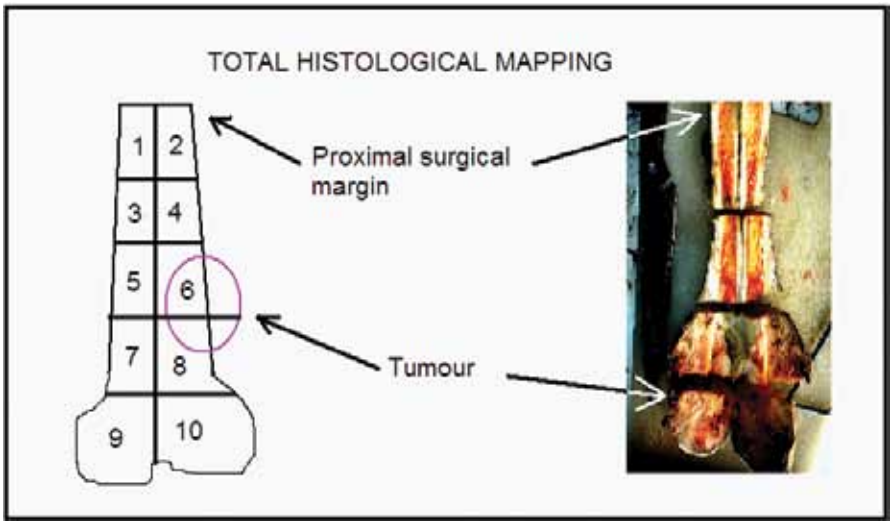

Figure 1: *Total Histological Mapping Procedure*

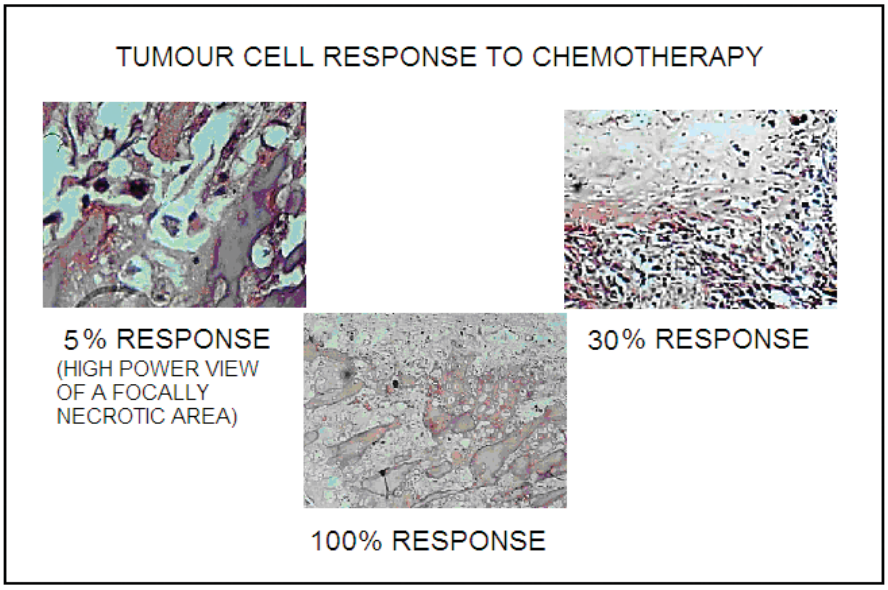

Figure 2: *Tumour Cell Response to the Chemotherapy*

RESULTS

Four patients were studied for response to neoadjuvant chemotherapy. They included three males and one female. The age group ranged from 12 to 19 years. All of the cases were high grade central conventional type and located in the distal femur. Three cases were of the osteoblastic variant and one was the chondroblastic variants. Two cases showed good response and two cases showed poor response (Table 1).

Although the number of patients is very limited, half of them were good responders. Low power scanning of the histology section was done to assess the effect of chemotherapy on the tumour cells. Necrotic areas showed non-viable cellular debris, residual osteoid and bony trabeculae and scanty inflammatory cells, (fig. 2).

DISCUSSION

Most cases of osteosarcoma are now assumed to be systemic diseases on presentation even though no pulmonary secondaries are visualized by conventional or advanced imaging techniques like bone scans, spiral computed tomography (CT) scans, Thallium scintograms or magnetic resonance imaging (MRI). Rosen pioneered the use of neoadjuvant chemotherapy at the Memorial Sloan Kettering Hospital, New York.[4] This treatment strategy was developed almost accidentally as patients had to wait for a few months for surgery as their prosthesis were being custom made, and it was decided to offer them a course of preoperative chemotherapy to shrink their tumour mass. Prior to neoadjuvant chemotherapy surgery used alone had resulted in only 15-20% long term survival rates. There was recurrent pulmonary disease in 50% of the cases within 6 months. This led Marina to raise the view that osteosarcoma shows micro metastases even with localized disease in the absence of any pulmonary disease detected by imaging modalities.[5] This has resulted in the use of systemic neoadjuvant chemotherapy to attack the microfoci of neoplasm followed by surgery. Surgical resection was preferred to radiation as osteosarcoma is generally not radiosensitive. The response to chemotherapy is currently the most sensitive indicator of long survival. Different authors have used different scales of grading. The different histological criteria that have been used by different authors to study the response of the sarcoma cells to the chemotherapy in various other centers are listed in Table 2.

Grading of the response is also prone to inter-observer variation errors. The time of surgery after chemotherapy can also affect the histological response. Current regimens

Table 1: Case results details

Case No.	Sex	Age	Variants *	% Necrosis	Inference
1	M	15	OB	5	Poor
2	F	12	CB	100	Good
3	M	17	OB	30	Poor
4	M	19	OB	100	Good

** OB = osteoblastoma, CB = chondroblastoma*

Table 2: Different Histological Grading Systems for Response to Neoadjuvant Chemotherapy for Osteosarcoma

Huvos	IV No tumour cells seen	III Scattered foci of tumour cells seen	II Areas of necrosis and tumour cells seen.	I Little or no tumour response seen		
Salzer-Kunts-chik	I No viable tumour cells	II Single tumour cells or clusters <0.5 cm	III Viable tumour cells < 10% seen	IV Viable tumour cells 10-50% seen	V Viable tumour cells >50% seen	VI No tumour response seen
Picci	Total tumor response	Good tumour response	Fair tumour response	Poor tumour response		

use 10-12 weeks of chemotherapy preoperatively. It is now widely accepted that >90 % necrosis is good response and <90 % response is poor response.[6-8] Good responders to neoadjuvant chemotherapy show 80-90 % long term survival (more than 10 years). Poor responders show only 15 % long term survival. The use of multidisciplinary and multimodality therapy has resulted in disease free survival of 60-80 %. Functional limb sparing surgery can be used in more than 80 % of patients. Bacci et al report a 60% good response to neoadjuvant chemotherapy with good response seen especially in the fibroblastic and telangiectic variants. Chondroblastic variant showed poor long term survival.[9] Our single chondroblastic variant showed good initial response to the chemotherapy. Long term follow up is yet to be studied. This case study reveals a 50% good response rate, and these patients were treated by limb sparing surgery. Both good function and long term survival is anticipated in these cases.

CONCLUSION

From this study it is expected that more bone sarcomas will be managed by limb sparing surgery in Nepal in the future.

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