PATHOLOGICAL ASSESSMENTOF TUMOR RESPONSE IN A NEO-ADJUVANT THERAPY TREATED RESECTIONS FOR OSTEOSARCOMAS

Syed Saad Gardezi, Iftikhar Ali Rana, Asif Loya, Sajid Mushtaq, Noreen Akhter, Muhammad Tariq Mehmood

Shaukat Khanum Memorial Cancer Hospital Lahore Pakistan

ABSTRACT

Objective: To assess of the pathologic response of patients of osteosarcoma, after neoadjuvant chemotherapy.
Study Design: Descriptive study.
Place and Duration of Study: Shaukat Khanum Memorial Cancer Hospital & Research Centre, Lahore from Jan 2016 to Aug 2016.
Material and Methods: A total of 60 cases of osteosarcoma found suitable by inclusion criteria were included in this study. Demographic details such as name, sex and age were collected. All specimens were grossed and staged according to CAP guidelines. Tumor response was assessed by two pathologists and graded as good and poor response.
Results: Sixty percent (n=36) of patients were between 7-18 years of age while 40% (n=24) of patients were between 19-45 years of age. Mean age was 17.65 years. A total of 58.33% (n=35) of patients were males and 41.67% (n=25) of patients were females. Thirty percent (n=18) of the patients had good response, while 70% (n=42) of patients had poor response to chemotherapy.
Conclusion: We concluded that the assessment of pathologic response of osteosarcoma after neoadjuvant chemotherapy in terms of good response and poor response is a useful tool for the pathologist and the oncologist. It gives us useful information regarding patient's response to neoadjuvant chemo radiotherapy that also helps in determining the further management and overall survival rate of the patient.

Keywords: Chemotherapy response, Osteosarcoma.

INTRODUCTION

Osteosarcoma is one of the most common primary bone malignancies, representing approximately 55% of childhood & adolescent malignant bone tumors[1]. The peak frequency occurring during 2nd decade of life; 60% of patients are younger than 25 years at the time of diagnosis and there is male predilection. Although osteosarcoma can arise in any bone, the favored sites are metaphysis of long bones. In Pakistan osteosarcoma, represents approximately 55% of childhood & adolescent malignant bone tumors & peak frequency occurs in 2nd & 3rd decades of life[2]. According to Shaukat Khanum cancer hospital & research Centre registry report, the incidence of osteosarcoma in Pakistan is 7.32% in patients less than 18 years of age[3].

Current management for biopsy proven high grade osteosarcoma requires a combination of surgical resection and systemic chemotherapy, both neoadjuvant (prior to surgery) and adjuvant (after surgery)[4]. Doxorubicin, cisplatin & high dose methotrexate are considered standard treatment for osteosarcoma[5]. Surgery is generally performed within three weeks following completion of neoadjuvant chemotherapy (NACT)[6]. Pathological assessment of the treatment response is very important for objective assignment of the tumor response & prognosis.

Recent data has shown that NACT not only show significant tumor regression but also improves local control and long term survival. O'Kane *et al* studied 62 patients to assess the tumor regression in terms of tumor response. In his study 33 patients demonstrated good response (≥90% necrosis) & 29 patients showed poor response (<90% necrosis)[7].

Correspondence: Dr Syed Saad Gardezi, Dept of Histopathology, Shaukat Khanum Memorial Cancer Hospital Lahore Pakistan
Email: saadgardezi@gmail.com
Received: 25 Jul 2017; revised received: 21 Nov 2017; accepted: 18 Dec 2017

Above mentioned data is predominantly derived from studies done on western population. No such study has yet been conducted on Pakistani population. Our rationale is to find out the response of tumor in patients of osteosarcoma treated with neoadjuvant chemotherapy with our demographic characteristics.

MATERIAL AND METHODS

The descriptive study was conducted at the department of Pathology, Shaukat Khanum Memorial Cancer Hospital & Research Centre, Lahore, from January 2016 to August 2016. Permission from ethical committee of the institution was taken before the start of the study.

A sample size of n=60 cases was calculated with 95% confidence level, 13% margin of error and taking expected percentage, poor response of patients with osteosarcoma i.e. 46.8% treated with neo-adjuvant chemotherapy and underwent subsequent amputation.

A total of 60 cases of osteosarcoma found suitable by inclusion criteria were included in this study. The cases were selected through non-probability consecutive sampling. Each case was given a case number and a medical record number. Demographic details such as name, sex and age was collected. All specimens were reviewed fresh for the sampling of soft tissue margins and examining the external features. Bone was frozen and cut longitudinally with a saw to obtain two greatest diameters of the tumor mass. The sections were decalcified and fixed in 10% buffered formalin, grossed and stained with Hematoxylin and Eosin. The whole longitudinal section of tumor was entirely submitted to assess the response. The morphology was reviewed by a histopathologist to establish the diagnosis.

Standard pathologic tumor staging was performed in accordance with the guidelines of the College of American Pathologists.

Tumors were divided into good response and poor response depending on tumor necrosis. 90% or more necrosis was categorized as good response and less than 90% response was categorized as poor response.

Frequencies and percentages were calculated for the selected variables i.e. response to treatment (good response and poor response.)

RESULTS

There were n=35 (58.33%) male patients and n=25 (41.67%) female patients. Mean age of the patients was 17.65 years. N=18 patients (30%) were found to have good treatment response, while n=42 patients (70%) of the patients had poor response (figure).

Table: Pathological evaluation of neoadjuvant chemotherapy treated amputations in osteosarcoma patients in terms of good response and poor response.

Treatment Response	n (Percentage)	Male	Female	≤18	≥19
Good Response	18 (30%)	13 (37.14%)	5 (20%)	13 (36.11%)	5 (20.83%)
Poor Response	42 (70%)	22 (62.86%)	20 (80%)	23 (63.88%)	19 (79.16%)
Total	60	35	25	36	24

Further details are discussed in table.

DISCUSSION

Osteosarcoma is the most common primary malignant bone tumor with a major peak incidence in adolescence and young adults and later in adults over the age of 65, accounts for less than 1 percent of all cancers diagnosed annually in the United States. Although osteosarcoma can arise in any bone, the favored sites are metaphysis of long bones. In Pakistan osteosarcoma, represents approximately 55% of childhood & adolescent malignant bone tumors & peak frequency occurs in 2nd & 3rd decades of life[2].

Prior to the introduction of chemotherapy in the 1970s, prognosis of osteosarcoma was dismal. Despite excellent local control rates with surgery, the vast majority of patients, even

those with seemingly localized disease, rapidly developed pulmonary metastases and died. Nowadays prognosis has improved dramatically since the introduction of chemotherapy in the late 1970s. Currently, using a multimodal approach consisting of neoadjuvant chemo-therapy followed by local surgical therapy and then postoperative ("adjuvant") chemotherapy, long-term, disease-free survival can be achieved in 60-70% of patients[8]. Doxorubicin, cisplatin & high dose methotrexate are considered standard treatment for osteosarcoma[5]. Neoadjuvant chemotherapy induces a number of morphologic changes that affect prognostication after curative surgery, thereby creating new challenges for surgical pathologists, particularly in evaluating morphologic changes and tumor response to pre-operative treatment. Surgical pathologists play an important role in determining the many facets of osteosarcoma patient care after neoadjuvant treatment.

Many systems have been proposed for recording of pathological response of tumor after the neoadjuvant chemotherapy. The currently used system was proposed by Huvos *et al*[7]. According to this system pathological response is assessed in terms of good response and poor response after neoadjuvant chemotherapy. Good response is defined when percentage of tumor necrosis after neoadjuvant chemotherapy is ≥90% while poor response is defined when percentage of tumor necrosis after neoadjuvant chemo-therapy is less than 90%.

Effect of neoadjuvant chemotherapy is well documented in western population however; no such study has been conducted in this geographical area. This study was planned to find out the response of tumor in patients of osteosarcoma in terms of good response and poor response treated with neoadjuvant chemotherapy with our demographic characteristics.

In our study, 60% (n=36) of patients were between 07-18 years of age while 40% (n=24) of patients were between 19-45 years of age, mean age was calculated as 17.65 years, 58.33% (n=35) of patients were males and 41.67% (n=25) of patients were females. Pathologic response of osteosarcoma in amputation specimens after neoadjuvant chemotherapy in terms of good response and poor response was recorded as 30% (n=18) of patients had good response, 70% (n=42) of patients had poor response.

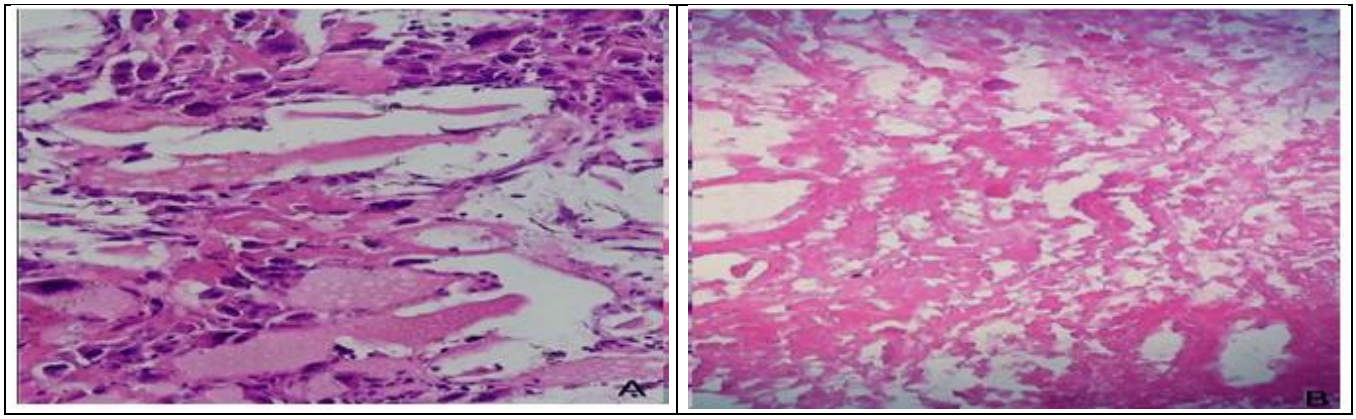

Figure: A) H&E 40X, showing osteosarcoma, poor response. Most of the tumor is still viable after chemotherapy. B) H&E 40X showing a case of osteosarcoma with good response. There is complete necrosis of the tumor with only visible outlines of tumor cells.

O'Kane *et al* and others studied 62 patients to assess the tumor regression in terms of tumor response. In their study the median of patients was 23 years with 95% of patients ≥18 years and 70% of patients included were male. After neoadjuvant chemotherapy 53.22% (n=33) of patients demonstrated good response (≥90% necrosis) & 46.77% (n=29) of patients showed poor response (<90% necrosis)[7].

Another study by Bacci and others[9] assessed and compared oncologic outcomes associated with the degree of pathologic response after chemotherapy in 1058 patients. In their study 59% (n=624) of patients showed good response and 41% (n=434) of patients revealed poor response. The 5-year overall survival rate was significantly higher (p=0.0001) in good responders p=0.0001 (68%) than in poor responders (52%).

Above mentioned data show that there is significant difference in patients of osteosarcoma in terms of percentage of good response after neoadjuvant chemotherapy in western population and in our demographic area. Inferior outcomes in our population may be explained by early age of presentation in our population (mean age of 17.56 years) as compared to the western population (mean age 23)[7], limitation of diagnostic facilities leading to delay in diagnosis and resultant increase in tumor related morbidities such as tumor size. Moreover low socioeconomic status, poor general health and nutritional deficiencies lead to decrease in tolerance of high dose chemotherapy which may result in poor response. Additional studies are required to determine pathogenesis of low response in our population taking the above mentioned variables into account.

CONCLUSION

We conclude that the assessment of pathologic response of osteosarcoma after neo-adjuvant chemotherapy in terms good response and poor response is a useful tool for the pathologist and the oncologist. It gives us useful information regarding patient's response to neoadjuvant chemo radiotherapy that also helps in determining the further management and overall survival rate of the patient.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

REFERENCES

1. Savage SA, Mirabello L. Using epidemiology and genomics to understand osteosarcoma etiology. Sarcoma 2011; 548151: 13.
2. Qureshi A, Ahmad Z, Azam M, Idrees R. Epidemiological data for common bone sarcomas. Asian Pac J Cancer Prev 2010; 11(2): 393-5.
3. Annual cancer registry report-2013. Shaukat Khanum Memorial Cancer Hospital & Research Center 2013; p05.
4. Rejniak KA, Lloyd MC, Reed DR, Bui MM. Diagnostic assessment of osteosarcoma chemoresistance based on virtual clinical trials. Med Hypotheses 2015; 85(3): 348-54.
5. Haddox CL, Han G, Anijar L, Binitie O, Letson GD, Bui MM, et al. Osteosarcoma in pediatric patients and young adults: A single institution retrospective review of presentation, therapy, and outcome. Sarcoma 2014; 402509.
6. Xu M, Xu SF, Yu XC. Clinical analysis of osteosarcoma patients treated with high-dose methotrexate-free neoadjuvant chemotherapy. Curr Oncol 2014; 21: e678–84.
7. O'Kane GM, Cadoo KA, Walsh EM, Emerson R, Dervan P, O'Keane C et al. Perioperative chemotherapy in the treatment of osteosarcoma: A 26-year single institution review. Clin Sarcoma Res 2015; 5: 17.
8. Dorothe C, Bielack SS. Current Strategies of Chemotherapy in Osteosarcoma. Intl Orthop 2006; 30(6): 445-51.
9. Geller DS, Gorlick R. Osteosarcoma: A review of diagnosis, management, and treatment strategies. Clin Adv Hematol Oncol 2010; 8(10): 705-18.