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Outcome of chemotherapy for adult soft tissue sarcomas in Jos, north central Nigeria

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Abstract: Background: Soft tissue sarcomas (STS) have a poor response to chemotherapy and reports have documented a 20% response rate. Chemotherapeutic regimens have evolved from the use of multiple drug combinations which were thought to be more efficacious, to high doses of single agent chemotherapy and targeted therapies. Predicting the response to chemotherapy in soft tissue sarcomas is difficult because even tumours of the same class exhibit different patterns of responsiveness to the same drugs. Single agent Adriamycin chemotherapy for soft tissue sarcomas is cheap and reputably gives comparable treatment outcomes to combination therapies. This study was therefore aimed at determining the outcome of management of soft tissue sarcomas with single agent Adriamycin chemotherapy. Patients and Method: This was a prospective analysis of consecutive patients managed for STS with single agent Adriamycin at the Jos University Teaching Hospital from January 2000 to December 2009.Results: A total of 89 adult soft tissue sarcomas were managed in 49 males and 40 females (M: F=1.2:1). The mean age of the study population was 37.4 +/- 12.6 with age range of 18 to 85years.Forty patients (44.9%) could afford chemotherapy with single agent Adriamycin and formed the basis of this study while 49 (53.1%) could not afford chemotherapy. All the tumours were more than 5cm in size at presentation. Rhabdomyosarcoma was seen in 17 patients (42.5%), fibrosarcoma in 14 (35%), liposarcoma and dermatofibrosarcoma 4 (10%) each and one patient (2.5%) had synovial sarcoma. Response to chemotherapy was seen in seven patients (17.5%) and this was noticed within six weeks of chemotherapy. Conclusion: Response to chemotherapy with single agent Adriamycin for the treatment of soft tissue sarcomas is very poor and it is difficult to predict which patient will respond to this therapy in our setting. We therefore suggest that all patients with STS on single agent Adriamycin in resource scarce settings should have their treatment discontinued or changed to other chemotherapeutic combinations if there is no response to chemotherapy after six weeks.

Keywords: Single Agent Adriamycin, Soft Tissue Sarcomas, Outcome

1. Introduction

Generally speaking, soft tissue sarcomas (STS) have a poor response to chemotherapy and several reports have documented a 20% response rate.(1-2) The management of STS in resource scarce settings is fraught with so many challenges ranging from late presentation, difficulty in ascertaining the correct pathologic diagnosis(3) and inadequate access to appropriate treatment.(4-6) In these resource scarce settings, emphasis on prevention and treatment of infectious diseases like HIV/AIDS and malaria take up a major part of the national health budget and little or no attention is paid to cancer management. This implies that the patients with cancers are left to fend for themselves and this may contribute to the late presentation that we typically see.(7)

Late presentation in STS connotes a locally advanced or metastatic disease that is largely treated with regional or systemic chemotherapy.(8-9)This mode of presentation is very common in our setting and surgery which is cheap and readily available cannot achieve cure. This leaves us with chemotherapy with different drug combinations as the only reliable treatment option. These chemotherapeutic regimens have evolved over time from the use of multiple drug combinations which were thought to be more efficacious (notable among which are

Ifosfamide+Cyclophosphamide and Etoposide), to high doses of single agent chemotherapy and even targeted therapies.(10-13)All these treatment options are very expensive and are associated with considerable toxicities warranting a careful selection of patients that should receive them. These tend to limit the dose of the drugs used and influence the different drug combinations.(14) Several studies have compared the efficacy of single agent adriamycin and other combination chemotherapies and have shown that adriamycin can be used as a single agent therapy in STS.(15-17)This Adriamycin is relatively cheap and available in our practice with tolerable side effects. It however requires periodic cardiac assessment during therapy to prevent cardio toxicity.

Predicting the response to chemotherapy in soft tissue sarcomas is difficult because even tumours of the same class exhibit different patterns of responsiveness to the same drugs. To reduce this difficulty, genomic profiling and molecular evaluation techniques have been used to differentiate the tumour types(18-19) while efforts are being made to assess their response to chemotherapy through advanced pathologic tests like the Ki-67 which is a cellular marker of somatic cell proliferation, cluster of differentiation 100 (CD100) that is useful for assessing the angiogenesis potential of the tumour and assay for the presence of multi-drug resistance proteins in some adult rhabdomyosarcomas.(20-22). The implication of these advancements is that if we could pre determine which patient will not respond to a particular type of chemotherapy, there will be no need to expose him to the toxic effects of such drugs. We will therefore rather treat him based on the pharmacogenomics of his tumour; this approach is referred to as personalized cancer therapy.(23-24)

These immunohistochemical techniques are not available in our practice and oral discussions with our pathologists suggest a 50% discordance in pathology reporting for soft tissue sarcomas compared with 26% reported by Shiraki et al.(25) This scenario makes it difficult to tell which patient with STS in our practice will benefit from neoadjuvant cytotoxic chemotherapy.

This study was therefore aimed at evaluating our experience with single agent Adriamycin chemotherapy in a resource scarce setting.

2. Patients and Method

This was a prospective analysis of consecutive patients managed for STS with single agent Adriamycin at the Jos University Teaching Hospital from January 2000 to December 2009.

Non consenting patients and those that were lost to follow up were excluded from the study.

3. Method

After obtaining an informed consent, consecutive patients with soft tissue sarcomas were assessed clinically, radiologically and pathologically with the aim of staging the tumour and deciding on its suitability for neo-adjuvant chemotherapy. Clinical measurements of the tumour coupled with laboratory and radiologic monitoring of metastatic lesions were done before commencement of chemotherapy and repeated as is necessary at 3 weeks (before next chemotherapy) and six weeks.

Chemoresponsiveness was defined as clinical reduction in maximum tumour diameter as measured from a reproducible point by 10% or more or complete regression of metastatic deposits at 3 weeks or 6 weeks after chemotherapy. Chemotherapy was stopped after two cycles in patients that showed no evidence of response or in whom the tumour progressed despite the chemotherapy.

Data was obtained on patient demographics, tumour location, histopathologic diagnosis, number of cycles of chemotherapy received and chemoresponsiveness. This data was analysed using Epi-info version 3.5.2 for means and standard deviations.

4. Results

A total of 89 adult soft tissue sarcomas were managed in 49 males and 40 females (M: F=1.2:1). The mean age of the study population was 37.4 +/- 12.6 with age range of 18 to 85years.Only forty patients (44.9%) could afford chemotherapy with single agent Adriamycin and formed the basis of this study while the remaining 49 (53.1%) did not have chemotherapy because they could not afford it.The mean tumour size was 7cm +/- 1.7 cm.Rhabdomyosarcoma was seen in 17 patients (42.5%), fibrosarcoma in 14 (35%),liposarcoma and dermatofibrosarcoma accounted for 4 (10%) each and one patient (2.5%) had synovial sarcoma. See table 1.

Table 1. *Shows Types of soft tissue sarcomas and the distribution of response to Adriamycin.*

Type of soft tissue sarcoma	Number	Distribution of responders to Adriamycin
Rhabdomyosarcoma	17	4
Fibrosarcoma	14	2
Liposarcoma	4	0
Dermatofibrosarcoma	4	0
Synovial sarcoma	1	1
Total	40	7

There was demonstrable clinical response to chemotherapy in 7 (17.5%) of the patients that had chemotherapy whereas the remaining 33 patients (82.5%) did not show any clinical response to chemotherapy. Six patients responded to the chemotherapy within three weeks of administration while one patient responded after four weeks.All responders were aged forty years and under with well differentiated tumours

The histopathology and location of the chemoresponsive tumours were as follows; 3 patients had alveolar rhabdomyosarcoma of the thighs, 2 had fibrosarcomas of the anterior abdominal wall, 1 patient had a retroperitoneal

pleomorphic rhabdomyosarcoma and 1 had synovial sarcoma of the left knee. (FIG 1)

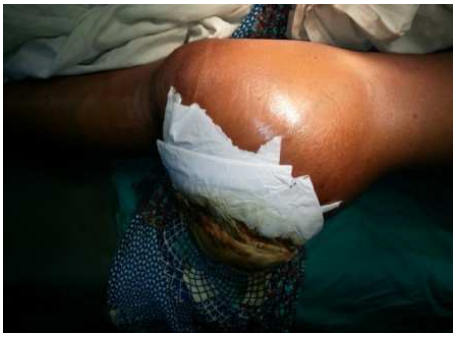

Fig. 1. *Synovial sarcoma of the left knee.*

5. Discussion

The main finding of this study was that only 17.5% responded to Adriamycin and this response was noticed within four to six weeks of administration in all the responders. This response rate is low compared to the 20 to 50% reported by Shinohara et al. This disparity can be explained by our small patient population in addition to the fact that we evaluated gross clinical response rather than the more sensitive radiological assessment using CT scan or MRI which were not available to us at the time of this study. That all the tumours in this study were more than 5cm in size may explain the low response rate since tumours of this size are associated with a poor prognosis as has been reported by Changchien et al.(26)

All patients that responded to chemotherapy in this study were below forty years old and had low grade tumours in agreement with reports from other researchers.(2, 25, 27)

This study also revealed that rhabdomyosarcoma was the most common soft tissue sarcoma in our practice and is in agreement with what Mandong et al reported from the same institution seven years earlier.(28)Even though rhabdomyosarcomas were the most chemo-responsive cancers in this study, only four responded to treatment out of 17 and three out of these responders had alveolar rhabdomyosarcomas. It is also curious to note that out of the nine alveolar rhabdomyosarcomas in this study, only three responded to chemotherapy. This observation tended to imply that it is difficult to predict which soft tissue sarcoma will respond to chemotherapy.

6. Conclusion

Response to chemotherapy with single agent Adriamycin for the treatment of soft tissue sarcomas is very poor and it is difficult to predict which patient will respond to this therapy in our setting. We therefore suggest that all patients with STS on single agent Adriamycin in resource scarce settings should have their treatment discontinued or changed to other chemotherapeutic combinations if there is no response to chemotherapy after six weeks.

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