Table of Contents

Original Articles

Phase II/III Randomized Controlled Trial of Concomitant Hyperfractionated Radiotherapy plus Cetuximab (Anti-EGFR Antibody) or Chemotherapy in Locally Advanced Head and Neck Cancer ..............................06
Khaled Al-Saleh, Mustafa El-Sherify, Reham Safwat, Amany Elbasmy, Jitendra Shete, Amany Hussein, Marwa Nazeeh, Ahmad Bedair

Betel Chewing: A New Analysis, In Vitro and In Vivo, of the Risk Factors in Oral Cancer .................................................................................................................................13
Roberto Menicagli, Ortensio Marotta, Maione Nunzia, Casotti Maria Teresa

Retrospective Analysis of Outcomes of Patients with Relapsed, Refractory and Metastatic Sarcomas who have received Metronomic Chemotherapy ..................................................................................22
Santhosh Kumar Devadas, Sripad Banavali

Does Adjuvant Chemotherapy for Locally Advanced Resectable Rectal Cancer treated with Neoadjuvant Chemoradiotherapy have an impact on survival? A Single Moroccan Institute Retrospective Study ..........................................................29
Youssef Seddik, Sami Aziz Brahmi, Said Aqir

A Multicenter Study of the Impact of Body Mass Index (BMI) on the incidence of Pathologic Complete Response (pCR) Among Saudi Patients with locally advanced Breast cancer (LABC) post Neoadjuvant Chemotherapy (NAC) ..................................................................................................................33

Effects of Tualang Honey on Cancer Related Fatigue: A Multicenter Open–label Trial of H&N Cancer Patients ..........................................................................................................................43
Viji Ramasamy, Norhafiza binti Mat Lazim, Baharudin Abdullah, Avatar Singh

The Incidence and Clinical Significance of Atypical Glandular Cells of Undetermined Significance on Cervical Pap Smears ............................................................................................................52
Ehab Al-Rayyan, Mitri Rashed, Maher Maaita, Sultan Qudah, Omar Taso, William Haddadin

Total or Subtotal Colectomy with Primary Anastomosis for Occlusive Left Colon Cancer: A Safe, Acceptable and Applicable Procedure ..................................................................................................57
William A. Nehmeh, Michel Gabriel, Ahmad Tarhini, Ghassan Chakhtoura, Riad Sarkis, Bassam Abboud, Roger Noun, Cyril Tohmé

Descriptive Study of Nasopharyngeal Carcinoma and Treatment Outcomes: An Eight Years Experience in Hadhramout National Cancer Centre, Yemen ...........................................................................61
Abdulrahman Ali Bahannan, Ahmed Mohammed Badheeb, Samir Yaslam Baothman

Review Articles

Preoperative Denosumab plus Surgery in the Management of Giant Cell Tumor of Bone: A Comprehensive Narrative Literature Review .............................................................................................................67
Ahmed Abu–Zaid, Sadiq Issa Alaqqili, Syed Osama Ahmad, Ibrahim Bin Hazzaa, Hani Alharbi

Case Reports

Malignant Pleural Mesothelioma: A Multi–Disciplinary Approach ..........................................................................................................................................................................................76
Muhammad Atif Mansha, Nasir Ali, Shaukat Ali, Nausheen Azam, Agha Muhammad Hammed Khan

Stage 4S Neuroblastoma: A Report of Two Cases Presenting with Extremes of Biological Behavior .................................................................................................................................81
Mohamed Mubarak, Arbinder Kumar Singal, Ashok Gawdi

Conference Highlights/Scientific Contributions

• News Notes ........................................................................................................................................................................85

• Advertisements ....................................................................................................................................................................88

• Scientific events in the GCC and the Arab World for 2019 ..................................................................................................89
Original Article

Retrospective Analysis of Outcomes of Patients with Relapsed, Refractory and Metastatic Sarcomas who have received Metronomic Chemotherapy.

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Abstract

Introduction: Paediatric soft tissue sarcoma treatments and outcomes have improved significantly in the last few decades. However, a significant number of patients still succumb to the disease. In low–middle income countries there are dual problems of advanced disease at presentation and financial burden leading to poor compliance to therapy. Hence, we designed a low–cost oral metronomic chemotherapy protocol for these patients and studied the responses and toxicities to therapy in a tertiary referral hospital.

Patients and Methods: This is retrospective, single institutional, observational study. We retrospectively reviewed data of patients with relapsed, refractory or metastatic soft tissue sarcoma (STS) [ Ewing Sarcoma (ES); Rhabdomyosarcoma (RMS) or other STS] who were treated with the metronomic protocol of oral Tamoxifen, Etoposide and Cyclophosphamide (TEC) during the period April 1998 to September 2013, at the Tata Memorial Hospital, Parel, Mumbai. Patients with ES and RMS were primarily treated on our Institutional protocols. The patients included in the analysis were those who had relapsed after the primary protocols and then treated with metronomic TEC protocol; or those with primary refractory or metastatic disease (RMS, ES) and received metronomic TEC therapy.

Results: 49 patients were enrolled. Among the 49 patients, 32 were diagnosed ES, 13 RMS and 4 other STS. For the whole cohort response rates (RR) were 59% and clinical benefit rate (CBR) was 79%. Patients in the study were grouped into the following subgroups. Systemic recurrent/relapsed disease (N=24), metastatic disease at presentation (N=15) and local disease (refractory/ recurrent) (N=10). None of the patients required blood or platelet support or admission for supportive care. The PFS for the above groups were 16.8 months, 12.5 months and 126.68 months respectively. This compares favorably with other historical cohorts in a similar setting.

Conclusions: This study provides a preliminary evidence efficacy and tolerability of metronomic chemotherapy in poor risk ES and RMS. It also demonstrates that with this low–cost low risk treatment few patients could go into long term remissions despite high disease burden.

Keywords: STS, Sarcoma, Metronomic, low–income, low–cost

Introduction

Sarcomas are one of the common malignancies in children and young adults and comprise of Soft Tissue Sarcomas (STS) and bone sarcomas. STS account for 7% to 8% of all cancers in children. The most common diagnostic subtype is Rhabdomyosarcoma (RMS) which accounts for 55% to 65% of all STS in childhood. Ewing’s Sarcoma (ES) includes osseous and extra–osseous Ewing’s tumors and is the second most common bone sarcoma after osteosarcoma. They are seen more often in younger children and young adults. Majority of patients with ES & RMS require aggressive neo–adjuvant chemotherapy followed by some form of definitive
local treatment, often both surgery and radiotherapy, followed by adjuvant chemotherapy to achieve good cure rates. Treatment usually lasts for 1 year. Nearly 15% of patients with RMS and 25% of patients with ES present with metastatic disease at first presentation. Five-year disease-free survival rates reported for patients with localized disease are up to 70%, while children with metastatic disease at diagnosis fare substantially worse with 5 years survival rates of 18% to 30%. The prognosis in patients with relapsed disease is even poorer, with the course of disease after recurrence usually being rapidly fatal. In a large retrospective cohort of patients of relapsed/refractory (local and systemic disease) ES, the survival was less than 20% despite conventional high dose chemotherapy. Survival and response to treatment after relapse of ES depends on the site of relapse (local versus distant; bony metastasis versus lung metastasis), and the time to relapse (<24 months versus > 24 months). Similarly, the outcomes after relapse in RMS are reported to be a dismal 10% long term survival.

Metronomic chemotherapy is the chronic administration of chemotherapy at low, minimally toxic doses on a frequent schedule of administration, with no prolonged drug–free breaks. Klement and Kamen proposed an alternative definition, suggesting that metronomic chemotherapy is the minimum biologically effective dose of a chemotherapeutic drug that, when given at a regular dosing regimen with no prolonged drug-free breaks, leads to antitumor activity. Although metronomic chemotherapy was initially defined as an antiangiogenic anticancer strategy, new mechanisms have since been identified, such as the restoration of the anticancer effect of the immune system. Therefore, metronomic chemotherapy can be regarded as a multi-targeted therapy. Although the rationale of metronomic chemotherapy is yet to be fully elucidated, the use of low–dose oral chemotherapy in the clinic has been mainly restricted to palliative purposes for many decades, both in adult and pediatric patients, with good response rates and sometimes lasting results.

Metronomic scheduling may be even more pertinent in Indian setting because of socio–economic and logistic issues related to intravenous chemotherapy and relative ease and low–cost of oral metronomic therapy.

In this retrospective analysis, we have evaluated the outcomes of patients with relapsed /refractory or metastatic disease with various sarcomas (mainly ES and RMS) who had received at least 3 months of oral metronomic chemotherapy protocol. The study period is from 1998 to 2013.

### Patients and Methods

#### Patients:

This is retrospective, single institutional, observational study. We retrospectively reviewed data of patients with relapsed, refractory or metastatic soft tissue sarcoma (STS) [Ewing’s Sarcoma (ES); Rhabdomyosarcoma RMS or other STS] who were treated with the metronomic protocol of oral Tamoxifen, Etoposide and Cyclophosphamide (TEC) during the period April 1998 to September 2013. All patients had histological confirmation of STS at the time of initial diagnosis. Approval of this retrospective study was obtained from the Institutional Review Board.

Patients with ES and RMS were primarily treated on our Institutional protocols (RCT II or EFT 2001 for ES & RCT II or IRS IV for RMS). Other STS patients were treated with standard ifosphamide / doxorubicin–based protocol. The patients included in the analysis were those who had relapsed after the primary protocols and then treated with metronomic TEC protocol; or those with primary refractory or metastatic disease (RMS, ES) and received metronomic TEC therapy.

#### Inclusion Criteria:

1) Patients with ES or RMS or other STS who had relapsed after at least 1 line of primary therapy.

OR

2) Patients with ES or RMS or other STS who had residual disease post primary treatment.

OR

3) Patients with ES or RMS who had metastatic disease at time of initial diagnosis and were unsuitable for definitive curative therapy.

#### Exclusion Criteria:

1) Patients with above inclusion criteria, but did not receive the oral metronomic TEC protocol.

2) Patients with above inclusion criteria and started on TEC therapy, but took less than 3 months of the oral metronomic treatment.

#### Treatment:

All treatments were given orally on an outpatient basis. It consisted of oral Tamoxifen 40 mg/m² divided twice daily every day at least for 1 year. Both Etoposide and Cyclophosphamide were also given orally at dose of 50 mg/m² for 21 days every 28 days, for a total of 12 cycles (1 year). These doses were capped at maximum of 1.5 m².
Metronomic Chemotherapy in Soft Tissue Sarcoma, Santhosh Kumar Devadas, et. al.

**Primary Outcome:**
- Overall Survival

**Secondary Outcome:**
- Progression free survival
- Responses (PR + CR)
- Clinical benefit Rate (PR+CR+SD)
- Toxicity

**Assessment of Response and Toxicity:**

All case files of patients with ES, RMS, and STS fulfilling the inclusion and exclusion criteria were reviewed retrospectively.

Medical records were reviewed for symptoms, examination findings, laboratory investigations and treatment done outside, if any, prior to presentation to our hospital. The investigations done at our hospital to confirm the diagnosis, to stage the disease and to risk stratify the patients were collected. Treatment given at our hospital was recorded, including chemotherapy regimen, number of chemotherapy cycles, second and subsequent lines of treatment, if any and radiation. The response to each line of treatment was recorded from the charts. The investigations done for interim response assessment and end of treatment response were recorded.

In case of a relapse, the investigations done for re-staging and response assessment were recorded along with the treatment given. All patients have standard tumor imaging done using CT, MRI, bone scan, or PET–CT as indicated. Physical examination and laboratory evaluations were performed at regular intervals. Patient’s disease status till the last follow up was recorded. Date of relapse/death if any and last follow up was recorded.

Overall survival (OS) was calculated from date of diagnosis to death due to any cause or last follow-up.

Post-relapse OS was defined as time interval from start date of metronomic therapy to the date of death or last follow-up date. Progression free survival (PFS) was calculated from date of start of metronomic therapy to disease progression or death due to any cause.

Tumor responses were classified according to the RECIST 1.1 criteria.14

**Statistics:**

Survival curves were plotted with Kaplan–Meier methodology. Cox–proportional hazards model has been used to analyze the effect of different variables on survival (OS and PFS). Descriptive statistics was used for analysis of demographic variable, disease characteristics and response rates. Patients who were lost to follow up after therapy were censored as alive at their last follow up. Patients who had disease progression or had only partial response at the end of therapy and were lost to follow-up were censored as progressed and dead at their last available follow-up. Data was analyzed using the SPSS program version 20.

**Results**

A total of 49 patients were included in the study. Among them 29 were male and 20 were female. Median age was 18 years at the start of metronomic chemotherapy, with age range between 3 years and 46 years. Twenty–six patients (53%) were pediatric (age<18) and 23 patients (47%) patients were adult (age>18).

Thirty–two (65.3%) patients were of PNET/ES, 13(26.5%) patients of RMS (7–ERMS and 6–ARMS). Other sarcomas were 4(8.2%) in number (epithelioid sarcoma 1, leiomyosarcoma 1, spindle cell sarcoma 1, synovial sarcoma 1).

Primary site was categorized based on broad site of origin as follows: Soft tissue–23(47.0%), Long bone–13(26.5%), Flat bone–8(16.3%), Chest Wall–5(10.2%).

Patients received metronomic chemotherapy in two settings (curative versus palliative intent)

1) Patients have undergone complete resection or curative radiotherapy (RT) to local /metastatic disease, followed by metronomic therapy as maintenance therapy in view of high risk of relapse or patients with residual disease after initial definitive therapy (chemotherapy and local therapy which includes surgery or RT or both) with a curative intent.

2) Patients who have high systemic disease burden not amenable to definitive therapy have received metronomic chemotherapy with palliative intent.

Based on the treatment setting (curative/maintenance versus palliative) patients were sub grouped as per Table 1:

<table>
<thead>
<tr>
<th>Maintenance metronomic chemotherapy after definitive therapy with curative intent</th>
<th>Metronomic chemotherapy with palliative intent</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent Systemic disease</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>Metastatic disease at presentation</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>Local Refractory/Recurrent disease</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
<td>30</td>
</tr>
</tbody>
</table>

Table 1. Clinical setting
Toxicity:
None of the patients required blood product support or admission for supportive care, when they were on metronomic chemotherapy.

Responses:
Best Clinical Response (BCR) was defined as best radiological response obtained with an imaging technique (CECT/PET-CT), at any point after starting metronomic chemotherapy, (either as maintenance after definitive local therapy or as therapy upfront for metastatic disease or as therapy for relapsed disease without giving any local therapy). Best clinical response based on disease categories are described in Table 2.

When patients were stratified based on disease categories (upfront metastatic disease versus recurrent disease systemic versus locally recurrent/residual disease. Outcomes were best for local disease with a median PFS of 126.68 months. For patients with primary metastatic disease median PFS was 16.8 months. For patients with systemic recurrence, median PFS was 12.35 months. Survival in local disease is just short of reaching statistical significance (p=0.08) (Figure 2).

Survival Analysis:
PFS was calculated from the start of metronomic chemotherapy to disease progression or death, or loss of follow up with disease. Median PFS for the whole group was 22 months (Figure 1).

Table 2. Response rates

<table>
<thead>
<tr>
<th>DISEASE CATEGORIES</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>RR</th>
<th>CBR (SD+CR+PR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RECURRENT SYSTEMIC DISEASE (24)</td>
<td>11</td>
<td>3</td>
<td>5</td>
<td>5</td>
<td>58%</td>
<td>79%</td>
</tr>
<tr>
<td>METASTATIC DISEASE AT PRESENTATION (15)</td>
<td>2</td>
<td>4</td>
<td>5</td>
<td>4</td>
<td>40%</td>
<td>73%</td>
</tr>
<tr>
<td>LOCAL DISEASE (REFRACTORY/RECURRENT) – (10)</td>
<td>8</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>90%</td>
<td>90%</td>
</tr>
<tr>
<td>TOTAL = 49</td>
<td>21</td>
<td>8</td>
<td>10</td>
<td>10</td>
<td>59%</td>
<td>79%</td>
</tr>
</tbody>
</table>

Figure 2. Progression free survival when patients stratified by clinical setting

Overall Survival:
At the time of analysis 18/49 patients have died. 16 patients were alive with disease, (this includes patients who have received metronomic chemotherapy upfront), and 15 patients were alive without disease.
- Median follow up of the entire group is 45.76 months (4.16 years).
- Median OS from start of metronomic chemotherapy –34.2 months (2.85 years) –(Figure 3)
When patients were stratified based on categories namely—upfront metastatic disease versus recurrent disease systemic versus locally recurrent/residual disease. Outcomes were best for local disease with a median OS of 138.87 months (11.57 years). For patients with primary metastatic disease median OS was 22.08 months (1.84 years). For patients with systemic recurrence median OS was 26.184 months (2.18 years). Survival in local disease is just short of reaching statistical significance (p=0.075) (Fig-4).

is even poorer, with the course of disease after recurrence usually being rapidly fatal. Even HDCT with HSCT does not increase the 5 years survival in these patients as a group. Presently none of the standard therapies have really helped us improve the outcome in patient with metastatic, refractory/relapsed sarcomas and there is no standard of care for these patients after failing fist-line standard therapies. This even prompted the UK group to suggest that such patients should be considered for novel therapy or should get treated with palliative treatment such as local radiotherapy or relatively non–toxic chemotherapy such as oral etoposide or cyclophosphamide.

The use of oral administration by our metronomic protocol gave us improved quality of life (QOL) and less resource utilization. In relapse/refractory/metastatic disease, the use of oral tamoxifen, etoposide and cyclophosphamide in patients with ES, RMS, and other STS, has yielded a Response Rate (RR) for the entire group (including local treatment, if received) of 59% with a Clinical Benefit Ratio (CBR) of 79%.

Though 4 of the 49 patients had non–RMS–STS, majority of the patients had either ES or RMS. Treatment consisted of oral combination protocol of TEC which was given on out–patient basis. In responding patients tamoxifen was continued post stopping of etoposide and cyclophosphamide as a single agent. Some patients who relapsed on TEC protocol received salvage therapies and some of these were again restarted on TEC protocol.

The median PFS and OS from start of metronomic therapy is 22 months and 69.6 months respectively for the entire group. This is better than many of the results published with much more aggressive therapies involving IV administration of drugs as well as requiring in–patient admission. Patients were stratified based on age, sex, site of primary tumour primary tumor (long bone vs flat bone versus, soft tissue versus chest wall), diagnosis (ES versus RMS versus OTHERS), duration of metronomic chemotherapy (<12 months versus> 12 months). There was no significant difference in PFS or OS based on these stratification groups.

Discussion

At the outset it has to be emphasized that this is a retrospective analysis of data acquired over a period of time and has all the limitations of a retrospective study. Especially important is the fact that this is not a consecutive patient data. Patients were started on metronomic therapy on a palliative basis at the time of relapse and sent home. We have analyzed only those patients who came back for at least the first follow–up visit after 3 months. Also, interpretation of the results is limited by the lack of randomization studies and head to head comparison among the different salvage regimes.

Patients with metastatic sarcomas, both ES and RMS, fare substantially worse than those with localized disease at presentation, with 5 year survival rates of 18 to 30%. The prognosis in patients with relapsed/refractory disease is even poorer, with the course of disease after recurrence usually being rapidly fatal. Even HDCT with HSCT does not increase the 5 years survival in these patients as a group.

Presently none of the standard therapies have really helped us improve the outcome in patient with metastatic, refractory/relapsed sarcomas and there is no standard of care for these patients after failing first-line standard therapies. This even prompted the UK group to suggest that such patients should be considered for novel therapy or should get treated with palliative treatment such as local radiotherapy or relatively non–toxic chemotherapy such as oral etoposide or cyclophosphamide.

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Response rates ranged between 40% to 60% depending on whether patient was exposed to study treatment at recurrent or primary metastatic setting. These results compare favorably with findings from a recent phase 2 trial of an MTD gemcitabine–docetaxel combination that reported a 40% overall survival after 1 year of follow–up and two responses (one complete and one partial response) out of 19 patients with relapsing sarcoma. It also compares favorably to another recent study published by Raciborska A. et al, which used vincristine, irinotecan and temozolomide in patients with relapsed and refractory ES. The response rate was 68.1% with median time to progression of only 3.0 months.
(range 1.1 to 37.1 months). Very importantly, though none of our patients underwent autologous HSCT, 4/5 surviving patients in this series were transplanted after responding to VIT chemotherapy. Similarly, a recent phase 2 study using a monoclonal antibody to the insulin-like growth factor 1 receptor in patients with recurrent or refractory Ewing’s sarcoma family of tumors reported a 14% response rate and a median overall survival of 10.4 months.\(^{16}\)

The median PFS and OS was 12.35 months and 26.18 months for patients respectively with systemic recurrence vs. 16.8 months and 22.08 months respectively for patients with locally recurrent/residual disease. The survival in local disease is just short of reaching statistical significance (P=0.08)\(^{18,19}\)

Metronomic therapies are being used more frequently because of the ease of administration, excellent cost effectiveness and maintaining Quality of Life (QOL). A pilot study of low dose anti-angiogenic chemotherapy in combination with standard chemotherapy for patients with newly diagnosed metastatic ES by COG showed an overall 24 months EFS of 35%. Whereas an OS advantage was not observed when compared to historical controls, the 2–year EFS of patient with pulmonary metastasis only was better than expected at 71%.\(^{17}\) Previous studies have shown 2–year survival rates of 31% and 36% for this group.\(^{18,19}\) Recent data shows that oral administration of irinotecan can result in similar SN-38 systemic exposures through IV administration thus facilitating the use of may be oral irinotecan and oral temozolomide in patients with relapsed/metastatic sarcomas, with improved QOL and less resource utilization.\(^{20}\)

Thus, this oral metronomic therapy was well tolerated and could be given on an outpatient basis with minimal supportive care. Patients could take the same at their place of residence. None of the patients required blood or platelet support or admission for supportive care. The per month cost of this treatment is approximately Rs. 1500 (~30 USD) as per current currency rates which is same as a dollar a day treatment as suggested by Dr. Kerr\(^{21}\) and much less than most of the aggressive protocols used in this setting. At the same time, the response rates, and especially the median PFS and OS are much better than that reported for many relapse protocols.

Considering the response in patients with metastatic disease at presentation as well as in patients with refractory disease, and especially the fact that the outcome was best (median OS of 126.28 months) for patients with minimal residual disease, we are planning to study this protocol in patients with higher risk of relapse (patients with metastatic disease at presentation; patients with higher tumor load at presentation) upfront after 6 months of intensive therapy as maintenance therapy for 12 to 18 months.

One of the challenges is to propose an affordable, accessible, safe, and effective treatment for patients with cancer living in Low and Middle–Income Countries (LMICs). The present strategies and standards of care in developed countries mostly rely on high–dose chemotherapy or targeted therapies and, although appealing for their efficacy and innovation, are not optimal for LMICs because of their cost, toxicities, and the complex infrastructure and technology needed. Metronomics—the combination of metronomic chemo–therapy and drug repositioning—might provide a way to overcome some of the major constraints associated with cancer treatment in developing countries and might represent a promising alternative strategy for patients with cancer living in LMICs.

**Conclusion**

This study provides a preliminary evidence efficacy and tolerability of metronomic chemotherapy in poor risk ES and RMS. It also demonstrates that with this low–cost low risk treatment few patients could go into long term remissions despite high disease burden. When given as maintenance therapy it shows excellent long–term outcomes.

Conclusions drawn from this study will stimulate further research which will increase our understanding of paediatric soft tissue sarcoma and metronomic low dose chemotherapy.

**References**