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ORIGINAL ARTICLE

METRONOMIC CONTINUOUS ORAL CYCLOPHOSPHAMIDE (CPM) AS SECOND AND FURTHER LINE IN METASTATIC SOFT TISSUE SARCOMAS (STS) OF THE ADULT

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ABSTRACT

In metastatic soft tissue sarcomas (mSTS) second and further line of therapy are poorly defined. However many patients (pts), after first line therapy including Antracyclines progress in their disease and ask to be treated. Oral cyclophosphamide (CPM) was already used in breast cancer, prostate cancer and in one study in mSTS with contrasting results. Aim of our study was to define the feasibility, tolerability and activity of oral CPM as second and further line chemotherapy in mSTS patients: 45 pts (19 M; 26 F) median age 60 (32-81), with pretreated mSTS were included. Oral CPM was given daily at total dose of 50 mg/day without interruption excepted for toxicity or progressive disease. Results: leiomyosarcoma 12, liposarcoma 10, MPNST 5, synovialsarcoma 4, indifferentiated sarcoma 4, other rarer subtypes 10. Sites of the primary tumor were: extremities 21, retroperitoneum 19, trunk 5.41 pts were metastatic, 4 locally relapsed. All 45 pts were pretreated with chemotherapy (17 were in II line, 18 in III line, 8 in IV line, 2 in V line). Median PS (ECOG) was 2. Median duration of therapy was 4.4 months (from 1 to 38 months). The 6-month PFS rate was 46%.
Treatment was well tolerated: neutropenia grade 2 in 1 case, fatigue grade 2 in 7 patients, nausea grade 1-2 in 22 cases. No grade 3-4 side effects were recorded.

Twenty two stable disease were recorded. No partial or complete responses were seen.
The median OS was 10.2 months [95% CI: 6.4; 13.2].
The 6-month OS rate was 64% and 32% at one year.
Oral CPM showed a mild activity and good tolerability in pretreated mSTS. It could be an appropriate solution as second and further line therapy and in unfit or elderly patients.

KEY WORDS

Metastatic soft tissue sarcomas; oral cyclophosphamide; metronomic therapy; chemotherapy; angiogenesis.

IMPACT STATEMENT

This phase II monoinstitutional study evaluates the activity as second and further line of therapy of metronomic cyclophosphamide in metastatic soft tissue sarcomas. The results obtained showed a stabilization of the disease in most cases and a good profile of toxicity.

INTRODUCTION

Soft tissue sarcomas (STS) are a heterogeneous group of mesenchymal malignancies diagnosed in approximately 2,500 patients in Italy each year (1) and with 5 years median survival of 53% (2).
More than 70 histologic subtypes are recognized, many of them harboring molecular subtypes with specific biological behavior (3, 4). As localized disease STS can be cured in a multidisciplinary approach in 75% of the cases with surgical intervention + radio and chemotherapy (5).
Unfortunately, STS metastasize mostly in the lung, and less frequently in liver and bone (6). When metastatic, the median survival is around 12 months and no effective therapy has been found until now (5).
Standard Chemotherapy is based on anthracyclines ± Ifosfamide as first-line treatment but the PFS is about 4 months (5-7).
After failure of anthracyclines, second line therapy includes trabectedin in lipo and leiomyosarcoma (7), HD Ifosfamide in undifferentiated sarcoma, liposarcoma and synovial sarcoma (8), taxanes in angiosarcoma (9).
Third line therapy can be an option in good performance status patients, but the unique end point is palliation.
Pazopanib as antiangiogenic agent has demonstrated some activity in this setting in non-adipocytic sarcoma (10), but few other drugs can be adopted: Eribulin in liposarcoma (11), Gemcitabine and Dacarbazine in leiomyosarcoma (12). Metronomic therapy can be an option. Metronomic chemotherapy (MC) is the regular administration of low-dose antitumoral drugs for a prolonged period of time with minimal or without drug-free intervals (12-15).
It differs from conventional cytotoxic chemotherapy in three main aspects:

1. MC has no direct antiproliferative effect but targets tumor growth by blocking angiogenesis and enhancing the host immune response through depletion of tumor-associated endothelial and regulatory T cells (16, 17).
2. MC is not based on MTD (Maximum tolerated dose) but on the equation time x dose (12-15).
3. MC lacks major toxicities following acute exposition to the drug (14, 15).

One of the most extensively studied metronomic chemotherapy uses the alkylating agent cyclophosphamide (CPM) alone or in combination, which can be administered on continuous schedule (12-16, 18-22).
In this study we investigated the role of metronomic CPM as second as well further line palliative treatment in patients with metastatic STS.

PATIENTS AND METHODS

From 2015 to 2018, 45 patients (19 males and 26 females) with metastatic soft tissue sarcoma were admitted at the Oncology Department of San Giovanni Bosco Hospital in Turin, Italy, for second or further line palliative therapy with metronomic CPM.
For all patients, a histological review was performed by the pathologist and the histological diagnosis was done according to 2013 WHO classification (3). The histological grade was determined following the FNCLCC grading system (23).
All the patients presented metastatic disease and

were pretreated with at least one line of chemotherapy. The study was approved by the local ethical committee. The patients characteristics are resumed in **table I**. Metronomic therapy consisted in CPM 50 mg/day as continuous oral administration. A blood cell count was performed every fifteen days. If neutrophils were below 1000/mm^3 or platelets < 100,000/mm^3, respectively, treatment was delayed until recovery. Oral Metoclopramide or Ondansetron were admitted in case of nausea and vomiting. The treatment was continued until disease progression, unacceptable toxicity or refusal of the Patient.

POPULATION'S CHARATERISTICS	
Number of patients	45
Median age	60 (32-81)
Sex	M 19 - F 26
PS median	2
METASTATIC DISEASE	
Syncronous	12
Metacronous	33
SITES OF METASTASIS	
Lung	31
Liver	6
Abdomen	8
SITE OF PRIMING STS	
Extremities	21
Retroperitoneum	19
Trunk	5
HISTOLOGY	
Leiomyosarcoma	12
Liposarcoma	10
MNPST	5
Synovial sarcoma	4
Undifferentiated sarcoma	4
Other histotypes	10
HISTOLOGICAL GRADE	
1	2
2	16
3	27
LINE OF THERAPY	
2	17
3	18
4	8
5	2
Metronomic regime CPM 50 mg/die	45

Table I. *Patients characteristics and patterns of treatment.*

The best response to treatment was evaluated according to RECIST criteria (24).

Progression-free survival (PFS) was defined as the time from the start of metronomic chemotherapy until disease progression, death or last patient contact. Overall survival (OS) was defined as the time from the start of metronomic chemotherapy until death or last patient contact.

Toxicity was classified according with NCI criteria (25).

Statistical analysis

The statistical analysis of demographics and clinical outcome is based on all data available up to the cutoff date of December 2018.

Survival rates were estimated with the use of the Kaplan–Meier method.

RESULTS

Baseline characteristics of the 45 patients, are summarized in **table I**.

Median age 60 years (range 32 -81), median PS was 2, but 5 patients had grade 3 according to ECOG classification.

The median number of metastatic sites was 1 (range: 1–3). Lung metastasis (31 cases) were prevalent. The most frequent STS histological types were: leiomyosarcoma 12, liposarcoma 10, MPNST 5, synovialsarcoma 4, undifferentiated sarcoma 4 , other rarer subtypes 10.

The histological grade was 3 in 27 cases, grade 2 in 16 cases, grade 1 in 2 cases following FNCLCC classification.

Primary tumor sites were: extremities 21 cases, retroperitoneum 19, trunk 5.

All the patients had received one or more line of chemotherapy before metronomic CTX: 17 were in second line, 18 in third, 8 in forth line, 2 in fifth line. 39/45 were pretreated with antracyclines as previous line of therapy. In 35 cases doxorubicin or epirubicin alone or in combination were administered as first line.

As presented in **table II** the median exposition to metronomic therapy was 4.4 months ranging from 1 to 38 months.

The median PFS was 4.0 months [95% CI: 2.6-9.8]. The 6-month PFS rate was 46%.

At the time of analysis, all 45 patients had died. All deaths were the result of progression of sarcoma. The median OS was 10.2 months [95% CI: 6.4 -13.2]. The 6-month OS rate was 64% and 32% at one year.

EFFICACY OUTCOMES	
Complete response	0
Partial response	0
Stable disease	22
Progressive disease	23
PFS median	4.0 months
6 months survival rate	64%
12 months survival rate	32%
Median overall survival	10.2 months
TOXICITY	
Neutropenia (G 2)	1
Fatigue (G 2)	7
Nausea and Vomiting (G 2)	22

Table II. *Results.*

No complete or partial responses were seen. Twenty two stable disease (48%) for a median PFS of 3.8 months were recorded.

DISCUSSION

Metronomic therapy opens a shift in the treatment of cancer.

In 1980's and 1990's an increasing dosing approach was dominant with escalating dose density and dose intensity made possible by blood stem cell support and a better knowledge of supportive care (14, 26).

The results of dose escalation lead to some results in lymphomas, myelomas, leukemia but not in solid tumors (14).

No results at all in STS (5, 6).

At the beginning of the new millennium, the concept of "cancer as chronic disease" started a different paradigm for dosing chemotherapy (1, 14).

Metronomic therapy is based on the concept to target neoangiogenesis, immunology and intracellular pathways of cancer cells, leading to a control on the growth, replication, neovascularization, and over the ability to metastasize of neoplastic cells (13-16).

The aims of the two therapies are clearly different:

- high dose therapy targets the replicating cells and kills them following the Skipper and Schabel rules (14, 27);
- metronomic therapy, on the contrary, determines the growth control, restores the apoptotic process and hampers the neoangiogenesis of the tumor slowing the metastatic diffusion (13-16).

Cyclophosphamide (CPM) is the most widely explored agent in metronomic approach since either in vitro studies or in clinical experience have demonstrated a long term antiangiogenetic effect with a lethal activity to endothelial cells (15, 16, 28-30).

Breast cancer (19, 31, 32), prostate cancer (18, 33, 34) are the two tumors with more studies on metronomic therapy.

Soft tissue sarcomas are rare tumors, with more than seventy different histological types (3).

Metastatic disease can be treated with chemotherapy with dismal results: 4-5 months PFS and 12 months Median Overall Survival (5, 6, 35).

One single institution experience with CPM 100 mg/day for 21 days every 28 days as second and further line of therapy in elderly or mild performance status patients suggests that Metronomic therapy may represent a choice in palliative setting (21).

Elderly and low performance status patients are often excluded from clinical studies and no specific option of therapy is available.

In our study we did not record complete or partial responses, but stable disease was seen in 48% of the patients. Median PFS of 4.0 months is superimposable to that of more toxic agents used in second line therapy (5-8, 10-12, 35).

In Mir and coll. study (22) the elderly STS patients were treated with CPM+ prednisone either as first or second line chemotherapy.

This French group had one complete and 6 partial response (ORR 26.6%) and 11 stable disease.

The median PFS was 6, 8 months and 1 year survival was 65.4%. Italiano and coll. used in a younger population (49 years as median age) etoposide with metronomic schedule (100 mg/day for 21 consecutive day every 4 weeks) as second line therapy after doxorubicin containing therapy (21).

The author recorded one partial response, 42% stable disease and 1-year overall survival of 31%.

All the other experiences in STS with metronomic CPM are reported in pediatric patients, but age-related histology vary. Embryonal rhabdomyosarcoma occurs almost exclusively in children and the percentage of response rate and survival are higher than in adults types of mSTS (36-41).

In animal model Ma and coll. introduced a multidosing metronomic therapy combining axitinib a TKI antiangiogenic drug + cyclophosphamide.

The combination showed a good activity both in vitro and in animal model and should be proposed

for future clinical trials (42). However, some experiences as case report were published with pazopanib, another TKI anti-VEGFR approved in metastatic STS at the dose of 800 mg/day (10).
Groenland and coll. reported two cases of patients with mSTS treated with pazopanib 200 mg/day personalized dose after grade 4 hematologic toxicity with standard dose. The serum active concentration of pazopanib was > 20,5 mg/L and demonstrated a relevant effect on the disease (43). CPM metronomic regime was developed to optimize the antitumor activity as well as to reduce toxicity (13-16, 21, 22).
As matter of fact in our study a low hematological and gastrointestinal side effects were recorded.
The same results were reported by Mir and coll. (22); whether in the study of Italiano and coll with metronomic etoposide published 4% grade 4 neutropenia (21). Limitation of our study are the heterogeneous population involved, with different age, performance status, dissimilar histology subtypes of STS and various lines of previous therapy.
As most studies investigating metronomic therapy in different tumors, our study is a single institution, non-randomized phase II trial.
Furthermore, in STS we recognize slow growing tumors with low proliferating cell population in contrast with highly aggressive tumors as angiosarcoma rapidly proliferating (3, 6). The stabilization of disease in some cases could be the consequence of the biological characteristics of the disease, rather than the effect of metronomic cyclophosphamide. In conclusion metronomic therapy could be considered a choice as second and further line therapy in mSTS.
Some aspects support metronomic therapy in specific clinical situations:

- stabilization of the disease for a variable period of time in heavily pretreated patients;
- low degree of toxicity;
- good compliance from the patients;
- possible synergistic effect with biological antiangiogenic therapy;
- low cost therapy.

On the contrary, some points need more investigations:

- the efficacious daily dose of metronomic CPM: 50 mg or 100 mg daily?
- continuous or interrupted treatment? (3 weeks in, 1 week out);
- CPM as single agent or combined with other drugs? (as vinorelbine or methotrexate in breast cancer);
- identification of biomarkers to predict the activity of the drug as antiangiogenic;
- the precise identification of the population who could benefit from metronomic therapy.

To face these problems the Italian Sarcoma cooperative Group (ISG) has designed a protocol comparing metronomic cyclophosphamide versus doxorubicin as first line treatment in elderly patients with mSTS. The end points are PFS, OS, ORR, toxicity and quality of life.
The ISG study is ongoing and the results could be useful to answer some of the open questions about metronomic therapy in mSTS in the specific population of the elderly patients.
In younger population and in specific subtypes of STS more specific studies are requested.

ETHICS

Fundings

There were no institutional or private fundings for this article.

Conflict of interests

The authors have declared no conflict of interests.

Availability of data and material

The data underlying this article are stored by the Data Manager Dr G. Cuomo.
at Ospedale San Giovanni Bosco (Turin, Italy) and can be shared just before a reasonable request to the corresponding author.

Authors' contribution

All the authors contributed equally to conception, data collection and discussion of this paper. CO: statistical analysis; AB and AC: writing.

Ethical approval

The study was approved by the Ethics Committee of the Humanitas Hospital of Gradenigo (Turin, Italy).

Consent to participate

Informed consent is attached to medical records.

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