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Efficacy of Palliative Metronomic Cyclophosphamide Chemotherapy: A Retrospective Analysis of 15 Years of Experience at CHU UCL Namur, Site Godinne

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Abstract

Background: The use of metronomic chemotherapy in routine clinical practice is still debated. This retrospective analysis was performed to evaluate the benefit-risk balance of this treatment in a palliative setting for unselected metastatic cancer patients.

Patients and Methods: We performed a retrospective analysis of all patients who received palliative metronomic Cyclophosphamide (mCTX) for metastatic solid tumors between 2005 and 2020 at our institution.

Results: A total of 82 patients received palliative mCTX at a dose of 50 to 150 mg/day either continuously or with a pause of 1 week per cycle. The most frequent diagnoses were colorectal (22%), prostate (20%), and ovarian cancer (16%). Nearly 20% of the heavily pretreated patients achieved clinical benefit at first assessment. Median duration of treatment was 2.5 months (range 0.1 to 118 months). Median progression-free survival was 2.5 months (range 0.1 to 118 months). Median overall survival was 4.6 months (range 0.2 to 130 months). These results increased with additional concomitant therapy and in patients with previous hormone therapy. Only 7% of patients stopped treatment due to toxicity.

Conclusion: This retrospective study shows that palliative mCTX has efficacy in some unselected patients, with low toxicity. Additional concomitant therapy is possible and offers an increased benefit. This treatment can be proposed in some patients, though it is unclear which patients will benefit most.

Keywords: Cyclophosphamide; Metronomic chemotherapy; Cancer metastasis; Palliative care

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Introduction

Metronomic chemotherapy began being used in oncology in the early 2000s [1]. Metronomic administration is defined as the administration of low doses of a drug or combination of drugs over prolonged periods of time, usually at a regular interval [2]. Low doses of chemotherapy allow it to be given daily, with no drug-free breaks, maintaining a sustained blood concentration [3].

The use of metronomic chemotherapy in routine clinical practice is still debated. In the metastatic setting, with heavily pre-treated patients, chronic side effects, such as hematotoxicity, neurotoxicity, or other damage to healthy proliferating tissues, often contraindicate the use of conventional therapy. Thus, alternatives are needed. Metronomic chemotherapy is a low-cost oral therapy that does not require regular daily clinic visits. Cyclophosphamide is the most commonly used drug in metronomic schedules.

No robust randomized phase III clinical trial has yet compared metronomic Cyclophosphamide (mCTX) to placebo in a palliative setting, and there have been only a few phase II trials. More data are needed to evaluate the real impact of mCTX in the palliative setting to avoid postponing best supportive care.

This retrospective analysis evaluated the benefit-risk balance of this treatment in a palliative setting for unselected metastatic cancer patients.

Patients and Methods

We performed a retrospective analysis of all consecutive patients who received palliative metronomic chemotherapy for metastatic solid tumors during the last 15 years at the University Hospital of the Catholic University of Louvain (CHU UCL Namur) site of Godinne. Patient identification and selection was carried out using the keynote "metronomic" or "métronomique" (in French) in the electronic medical file database of the Institution. Patients were identified in October 2020 and included any medical report since January 01st, 2005. We found 131 patients with the word "metronomic" in their electronic medical file. We excluded patients who had hematological malignancies (n=5 patients: 2 myeloma, 2 T-cell lymphomas, and 1 refractory anemia), had never taken the treatment (n=38), and were lost to follow-up at the time of the first prescription (n=3).

Data were collected for a total of 85 patients. Three patients received metronomic etoposide. All others received mCTX. For statistical power, we only took into consideration the 82 patients who received mCTX. From the medical files, we collected data on gender, age, Eastern Cooperative Oncology Group performance-status score (ECOG-PS; from 0 to 4, with higher numbers indicating greater disability) [4], primary tumor, histology, initial stage, all systemic, radiotherapeutic, or surgical therapies in localized and advanced disease, date of recurrence, dosage of mCTX, duration of treatment, any additional concomitant therapy for cancer, reason for stopping mCTX, results of assessments, and date of death.

We selected four outcomes: Clinical benefit, Overall Survival (OS), Progression-Free Survival (PFS), and duration of treatment. We defined patients who experienced a clinical benefit as the patients achieving a complete response, partial response, or stable disease. The OS was the time between beginning mCTX and death. The PFS was the time between beginning mCTX and disease progression or death. Lastly, the duration of treatment was the length of time during which the patient took mCTX.

Unfortunately, this retrospective study does not allow the measurement of quality of life, which is one of the most important parameters in this type of patient with very advanced disease.

Descriptive statistics were used to analyze patient characteristics (median, 95% Confidence Intervals [CIs], ranges). The associations between clinical benefit, OS, PFS, and predictor variables were calculated using the Cox proportional hazards model. Duration of treatment was analyzed using the Spearman correlation for quantitative variables and the Mann-Whitney test for categorical variables. A p-value <0.05 was considered significant. All statistical analyses were performed using the software R 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

The study was approved by the Ethical Committee of the CHU UCL Namur site Godinne.

Results and Discussion

This retrospective study analyzed all consecutive patients with advanced or metastatic solid cancers who took mCTX at the CHU UCL Namur site Godinne from January 2005 until October 2020. The median age of the 82 patients (36 women and 46 men) was 72 years (range 43 to 92 years). Initial ECOG-PS was 0 to 1 for 48 patients, 2 for 25 patients, and ≥ 3 for 5 patients. The three most frequent diagnoses were colorectal cancer (22%), prostate cancer (20%), and ovarian cancer (16%). Six patients had squamous cell carcinoma and five patients had neuroendocrine carcinoma. Fifty-four patients were initially treated with curative intent. These 54 patients had a median recurrence time of 20 months (range 2 months to 27 years). Thirty patients received neoadjuvant or adjuvant chemotherapy. All of these data are summarized in Table 1.

The median number of previous systemic lines of treatment for advanced disease was 4 (range 0 to 10 lines). Nearly 30% of patients received hormone therapy at least once; 50% of patients received local therapy for advanced disease before mCTX (radiotherapy, surgery, chemoembolization, or radioembolization).

We identified different dosages for mCTX. Nearly 50% of patients took 50 mg daily for 2 weeks, then 100 mg daily. Others took 50, 100, or 150 mg daily. Moreover, 88% of patients were taking the drug continuously, whereas 12% of patients had a drug-free break of 1 to 2 weeks per cycle of 3 to 5 weeks.

We noted that 32% of patients received concomitant therapy for cancer: 15% received local therapy, 1 of whom underwent surgery for metastasis and 11 patients' radiotherapy, mostly for analgesic purposes (9/11); and 17% of patients received systemic therapy, 7 patients were treated with denosumab or zoledronate, 3 with trastuzumab, 2 pertuzumab, 2 hormone therapy, 2 lanreotide, 1 bevacizumab, and 1 weekly oral methotrexate. Nearly 20% of the heavily pretreated patients achieved a clinical benefit at the first assessment; 1 patient (1%) achieved a complete response, 3 (4%) a partial response, and 12 (15%) stable disease (Table 2).

The median PFS (mPFS) was 2.5 months (range 0.1 to 118 months). The median OS (mOS) was 4.6 months (range 7 days to 130 months). Nine patients were still alive at the time of the analysis.

The median treatment duration was 2.5 months, with a maximal treatment duration of 118 months. The most common reasons for stopping mCTX were progressive disease (n=40 patients) and palliative care (n=22 patients). Only 7% of patients stopped treatment due to toxicity; 5% of patients were still taking mCTX at time of analysis, but 6% of patients were lost to follow-up.

Unsurprisingly, we found that patients who had concomitant therapy during mCTX treatment had a greater chance of achieving a clinical benefit, with an Odds Ratio (OR) of 0.26 (95% CI 0.08 to 0.80; p=0.02). Concomitant therapy also influenced the PFS (Hazard Ratio [HR] 0.36, 95% CI 0.2 to 0.65) and OS (HR 0.38, 95% CI 0.22 to 0.65; Figure 1). It also significantly prolonged the duration of mCTX therapy. Sex, age, diagnosis, and number of previous lines were not confounding factors for concomitant therapy. (Table 3 and Appendix: Table 1, 2).

We also found that patients who had received hormone therapy at least once during their treatment had a better risk of achieving a clinical benefit (OR 0.32, 95% CI 0.1 to 1; p=0.04). Previous hormonotherapy also prolonged the PFS (HR 0.42, 95% CI 0.23 to 0.74), OS (HR 0.49, 95% CI 0.29 to 0.85; Figure 2), and treatment duration. In addition, these patients had received significantly more previous lines of therapy than the others. (Table 3 and Appendix: Table 1, 2).

As expected, an initial ECOG-PS ≤ 1 significantly influenced the OS (HR 0.45, 95% CI 0.27 to 0.75) and the treatment duration. However, there was only a trend for improved clinical benefit (OR 0.31, 95% CI 0.07 to 1.1; p=0.092) and PFS (HR 0.65, 95% CI 0.38 to 1.08). (Table 3 and Appendix: Table 1, 2).

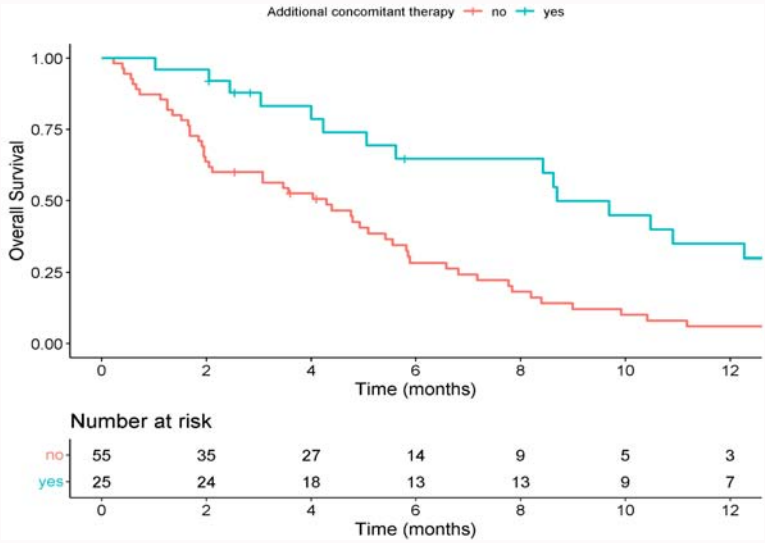

Figure 1: Overall Survival (OS) with and without additional concomitant therapy. Additional concomitant therapy prolonged OS with an HR of 0.38 (95% CI 0.22 to 0.65; p=0.0005).

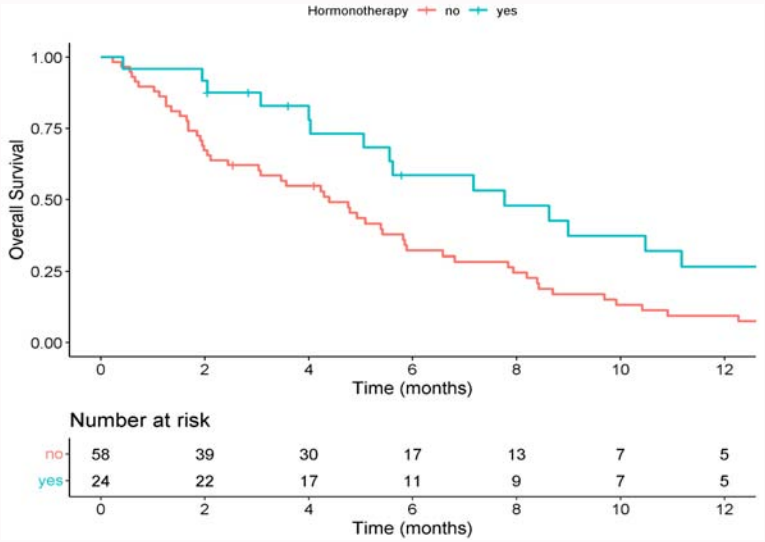

Figure 2: Overall Survival (OS) according to previous hormone therapy. Previous hormonotherapy prolonged OS with an HR of 0.49 (95% CI 0.29 to 0.85; p=0.01).

The three most frequent diagnoses (colorectal, prostate, and ovarian cancer) were not associated with improvement in the PFS or OS, but patients with ovarian cancer had a trend of greater clinical benefit, even if it was not significant (OR 0.3, 95% CI 0.08 to 1.16; p=0.069). (Table 3 and Appendix: Table 1).

There was no difference in the results for gender, initial stage (localized or primary advanced disease), having systemic therapy in the early setting, or the number of previous lines (>3 or <3). A long time between the onset of advanced disease and starting mCTX seems to increase the OS (HR 0.88, 95% CI 0.78 to 0.99; p=0.03). (Appendix: Table 1).

Overall, 20% of patients received systemic therapy after mCTX (chemotherapy of any kind), which was a predictive factor for OS (HR 0.48, 95% CI 0.27 to 0.86; p=0.01). We also observed that the older the patient, the longer the treatment (p=0.017). (Appendix: Table 1, 2).

In this retrospective study, we show that palliative mCTX has a clinical benefit for nearly 20% of unselected patients, with a mPFS of 2.5 months and mOS of 4.6 months. These are relevant results for very heavily pretreated patients and are comparable to previously reported trials.

In 2010, Penel et al. [5] published the results of a phase II trial in which 88 patients with progressive and advanced cancer were randomized to receive 50 mg mCTX twice a day or 160 mg megestrol acetate daily. The conclusion was in favor of mCTX, with a 2-month progression-free rate of 20%, which is very similar to our results. The mOS was 195 days. For gynecological tumor trials, Gupta et al. [6] reported a randomized phase II trial of 52 patients with advanced gynecological tumors who were randomized to 50 mg mCTX daily alone or with 400 mg celocoxib twice daily. They did not find significant differences between the two groups. Interestingly, 19% of the very heavily pretreated patients achieved clinical benefit. More recently, a retrospective cohort study of relapsed ovarian cancer patients taking mCTX at 50 or 100 mg daily also reported a partial response in 32% of patients and stable disease in 16%. The mPFS was 2.6 months and mOS 6 months. Toxicity was low [7] and, again, the

Table 1: Patient characteristics.

Characteristic	Number of patients Total: 82
Gender	
Male	46 (56%)
Female	36 (44%)
Age at the beginning of mCTX (years)	
Median	72
Range	43 - 92
ECOG-PS before metronomic cyclophosphamide (mCTX)	
0-1	48 (61%)
2	25 (32%)
3-4	5 (6%)
Diagnoses	
Colorectal cancer	18 (22%)
Prostate cancer	16 (20%)
Ovarian cancer	13 (16%)
Bilio-pancreatic cancer	9 (11%)
Breast cancer	5 (6%)
Esophageal cancer	5 (6%)
Others	16 (20%)
Initial stage	
0-III	42 (52%)
IV	39 (48%)
Previous chemotherapy in the early setting	30 (37%)
Previous therapy for advanced disease	
Chemotherapy	78 (95%)
Immunotherapy	2 (2%)
Radiotherapy	30 (37%)
Surgery	14 (17%)
Hormone therapy	24 (29%)
Number of previous lines for advanced disease	
0-1	9 (11%)
2	12 (15%)
≥ 3	61 (75%)
Dose of mCTX	
50 mg daily	29 (36%)
100 mg daily	8 (10%)
150 mg daily	4 (5%)
50 mg daily for 2 weeks then 100 mg daily	40 (49%)
Schedule of mCTX	
Continuous	72 (89%)
2 weeks out of 3 or 4	9 (11%)
Additional concomitant therapy	
Radiotherapy	11 (13%)
Surgery	1 (1%)
Systemic therapy	14 (17%)
Denosumab or zoledronate	7 (9%)
Trastuzumab ± pertuzumab	3 (4%)
Hormone therapy	2 (2%)
Lanreotide	2 (2%)
Bevacizumab	1 (1%)
Weekly oral methotrexate	1 (1%)
Systemic therapy after mCTX	16 (20%)

Table 2: Results.

PFS (months)	
Median	2.5
Range	0.1 - 118
OS (months)	
Median	4.6
Range	0.2 - 130
Duration of treatment (months)	
Median	2.5
Range	0.1 - 118
Best overall response	
Complete response	1 (1%)
Partial response	3 (4%)
Stable disease	12 (15%)
Progressive disease, palliative care, or death	62 (76%)
Toxicity	4 (5%)
Reasons for stopping mCTX	
Progressive disease	40 (49%)
Palliative care	22 (27%)
Death	3 (4%)
Lost to follow-up	5 (6%)
Toxicity	6 (7%)
Unrelated cardiac deficiency	1 (1%)
Still ongoing	4 (5%)

findings were very close to our results. Sharma et al. [8] reported a phase II trial of mCTX for platinum-resistant or refractory ovarian cancer. Patients were randomized for 50 mg mCTX daily plus (arm A and B) oral etoposide plus (for arm B only) oral pazopanib 400 mg per day. The mPFS was 5.1 months for arm B and 3.4 months for arm A (without pazopanib), and the mOS was not reached for arm B but was 11.2 months for arm A. Regarding prostate cancer, in a prospective phase II trial, Ladoire et al. treated metastatic castration-resistant prostate cancer patients with 50 mg mCTX daily and 10 mg prednisolone daily. They achieved a mPFS of 6 months and mOS of 11 months. In addition, quality of life increased for 43% of the patients [9]. In 2019, Caffo et al. reported the results of a retrospective trial with metastatic castration-resistant prostate cancer patients. In this series, the mPFS was 4 months and mOS 8.1 months [10].

Metronomic chemotherapy has many mechanisms of action; it acts not only through direct tumor cell killing or by inducing apoptosis, reducing metabolism, but it also has antiangiogenic properties and acts as an immunomodulator [11,12]. It is a good strategy to obtain a response, overcome resistance, and reduce side effects [13]. Tumor cells need oxygen and nutrients to proliferate. Therefore, they need continuous formation of new blood vessels, a process called angiogenesis. Antiangiogenic therapies are now commonly used in the treatment of neoplasia. Metronomic chemotherapy also has antiangiogenic properties, resulting in a significant decline in Vascular Endothelial Growth Factor (VEGF) levels, reduced tumor endothelial cell proliferation, and increased apoptosis [1,14]. It has also a direct cytotoxic effect on vascular proliferating endothelial cells [15]. The continuous drug intake does not allow endothelial cells to recover as seen in conventional chemotherapeutic schedules. The antiangiogenic properties are an independent mechanism of action of the chemotherapy and may have prolonged action, even when drug resistance of tumor cells occurs. This may explain why some patients achieve a long benefit from these regimens in the palliative setting [15].

It is now well known that the immune system plays a key role in the fight against cancer. mCTX also acts as an immunomodulator, initially reducing circulating regulatory T cells by more than 40% [16]. The conventional T cells and natural killer cells can then proliferate and kill tumor cells [17], restoring the immunological control of tumor progression.

In our trial, five factors correlated with clinical benefit, longer PFS, OS, and/or duration of treatment. The most significant factor was the presence of additional concomitant therapy, which correlated with all four outcomes. Gender, age, diagnosis, and number of previous lines were not confounding factors for concomitant therapy. The concomitant therapies were bisphosphonate (e.g., zoledronate), targeted therapies (e.g., trastuzumab, pertuzumab, and bevacizumab), hormone therapy, lanreotide, weekly oral methotrexate, radiotherapy, or surgery. We do not know the roles of mCTX and the additional

Table 3: Clinical benefit.

Characteristic	With clinical benefit[a] Total: 16	Without clinical benefit[b] Total: 66	Odds ratio (95% Confidence Interval)	P-value for odds ratio
Gender			0.99 [0.32;2.98]	0.9891
Male	9 (56%)	37 (56%)		
Female	7 (44%)	29 (44%)		
ECOG-PS at the beginning of mCTX			0.31 [0.07;1.1]	0.09242
High (≥ 2)	3 (19%)	30 (45%)		
Low (0-1)	11 (69%)	34 (52%)		
Diagnoses				
Colorectal cancer	2 (12%)	16 (24%)	2.24[0.55;15.24]	0.3186
Prostate cancer	4 (25%)	12 (18%)	0.67 [0.19;2.70]	0.5388
Ovarian cancer	5 (31%)	8 (12%)	0.30 [0.08;1.16]	0.06999
Initial stage			2.41 [0.78;8.38]	0.138
0-III	11 (69%)	31 (47%)		
IV	5 (31%)	34 (52%)		
Previous hormone therapy	8 (50%)	16 (24%)	0.32 [0.1;1]	0.04815
Number of previous lines for advanced disease			0.48 [0.14;1.49]	0.2196
Median	5	4		
Schedule of mCTX			1.02 [0.14;4.64]	0.9833
Continuous	14 (88%)	57 (86%)		
2 weeks out of 3 or 4	2 (12%)	8 (12%)		
Additional concomitant therapy	9 (56%)	16 (24%)	0.26 [0.08;0.8]	0.02011
Systemic therapy after mCTX	3 (19%)	13 (20%)	1.06 [0.29;5.12]	0.9317

[a]With clinical benefit means, at first assessment, patients achieved a complete response, partial response, or stable disease. [b]Without clinical benefit means all other patients

therapies in successful treatment, but we can infer from our data that it is relevant to combine mCTX with other therapies. There have been some trials with mCTX in association with other systemic treatments, even in an early setting [8,18].

Previous hormone therapy is the second most relevant variable. It also correlated with all of the outcomes. Among patients who took hormone therapy, 16 had prostate cancer, 4 breast cancer, 3 ovarian cancer, and 1 endometrial cancer. The 24 patients with hormone-sensitive neoplasia were compared mainly to colorectal (n=18), biliopancreatic (n=9), esophageal (n=5), and vesical (n=4) neoplasia. These malignancies are known to have a bad prognosis. We looked for confounding factors in this group of patients, but the only significant confounding factor was that patients who took hormone therapy had more previous lines of therapy than the others (p=0.002). There were also more men than women who took hormone therapy, and they were slightly older (both p>0.05). As discussed previously, several trials have suggested some efficacy of mCTX in prostate and gynecological cancer [7-10,19,20].

An interesting finding is the age at the beginning of mCTX therapy, as it correlated with the duration of treatment and the PFS. The older the patient, the longer the treatment (p=0.026). By the same token, the longer the time between diagnosis of advanced disease and beginning mCTX, the longer the treatment and OS. This does not correlate with the number of previous lines received for advanced disease but probably reflects the more indolent course of some diseases. Unsurprisingly, systemic therapy after mCTX increased the OS. In our series, 15% of patients had additional therapy after mCTX.

Finally, we did not find any correlation with gender, the initial disease stage, and previous systemic therapies (except hormonal). In addition, the efficacy was observed equally if the mCTX was taken continuously or with therapy breaks. The toxicity profile was good, with no grade 3 or 4 toxicity.

This is a retrospective trial with bias in patient selection. It was conducted in a single center with practices that may differ from other centers. Quality of life was not assessed. Our patient population was heterogeneous. There were a lot of different tumor types, previous lines of therapy, and concomitant therapies. In this palliative setting, a lot of patients died before having time to benefit from mCTX; 21 patients (26%) were on the treatment <1 month. Large prospective, randomized, multi-center studies are needed to confirm these findings.

Conclusion

This retrospective study shows that palliative mCTX has efficacy in some unselected highly pretreated patients, with nearly 20% experiencing clinical benefit. Toxicity is low. It seems that patients with initially hormone-sensitive disease will best respond to the treatment. Therefore, it may be relevant to combine mCTX with an additional concomitant therapy. We need large prospective randomized studies to confirm those findings and to assess quality of life. Thus, mCTX can be proposed in some palliative patients, though it is unclear which ones will benefit most.

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