 DOI: 10.18231/2455-6793.2017.0013

Metronomic oral cyclophosphamide (MOC) therapy in the recurrent and advanced ovarian cancer patients: a retrospective study

V. Arun Ramanan[1,*], K. Kalaichelvi.[2], S. Lakshminarasimhan[3]

[1]Resident, [2]Professor & HOD, Dept. of Medical Oncology, Madras Medical College, [3]Professor, Dept. of Medical Oncology, IOG, Madras Medical College, Chennai, Tamil Nadu

***Corresponding Author:**
Email: arun.ramanan81@gmail.com

Abstract

Introduction: To evaluate the efficacy of cycled oral cyclophosphamide therapy in recurrent and advanced ovarian cancer patients.
Materials and Method: Recurrent and advanced ovarian cancer patients who are unfit for intensive chemotherapy were prescribed oral cyclophosphamide at the dose of 50 mg twice daily for 10 days, cycled every 28 days. Treatment-related toxicity was assessed by National cancer institute – common terminology criteria for adverse events(NCI-CTCAE) and response to treatment were assessed by Response evaluation criteria in solid tumours (RECIST) and clinical assessment. Progression-free (PFS), and overall survival (OS) were assessed using Kaplan meier survival analysis.
Results: 71 patients of ovarian cancer admitted to our centre from January 2012 to March 2015 with mean age of 61.2±0.74 years were analyzed: 44 patients (61.9%) were platinum refractory/resistant, while 26 patients (36.6%) were platinum sensitive; 60 patients (84%) had received atleast one previous chemotherapy before starting MOC. The objective response rate (ORR) (complete and partial response) was 20%. Stable disease was seen in 22 patients (30.9%) and 17patients had response duration ≥6 months, 8 patients had continued response for more than 1 year. Progression during treatment was observed in 49 patients (69.01%). Median PFS was 5 months (range 2 – 25 months), and the 12-month PFS was 11%; and the 12-month OS was 26%
Median PFS for patients who responded to MOC was 9 months whereas 2 months for those who progressed (p = 0.01). Median OS of responding patients was 14 months whereas it was 8 months for patients progressive on MOC (p = 0.02). No significant toxicity was observed.
Conclusions: MOC is an effective therapy in the treatment of recurrent and advanced ovarian cancer patients, unfit for intensive chemotherapy.

Keywords: Recurrent and advanced ovarian cancer, Metronomic oral cyclophosphamide (MOC)

Introduction

Ovarian cancer remains the most lethal gynaecological malignancy with a 5-year survival rate of 25-30% in advanced stage disease.[1,2] In particular, patients recurring within 6 months from initial therapy exhibit low rates of response (4-23%) to salvage treatment, and a median overall survival of ~ 12 months.[2] Patients who recur >12 months after initial therapy are defined as platinum sensitive, and are usually re-challenged with platinum based chemotherapy.[3]

In the palliative scenario, frequent or even continuous administration of low dose chemotherapy (i.e. metronomic chemotherapy like cyclophosphamide, etoposide, celecoxib, bevacizumab) has gained much attention in recent years; indeed, this method of drug administration has been shown to be as active and, in some circumstances, even more efficacious than conventionally administered chemotherapy, with only negligible toxicity.[4-6] Antitumor activity induced by metronomic cyclophosphamide drug administration has been ascribed mainly to its anti-angiogenic effects.[5-7]

Materials and Method

Retrospective data analysis was done with 71 patients of epithelial ovarian cancer treated from January 2012 to March 2015 at the Department of Medical Oncology, in a tertiary hospital, Chennai. All patients had histologically documented epithelial ovarian cancer and were previously treated with at least one prior line of platinum based chemotherapy regimen and they had radiological evidence of recurrence or progression of disease. Pre-treatment evaluation included abdomino-pelvic CT, and serum CA 125 value. These patients were subjected to Metronomic therapy with single agent oral cyclophosphamide 50 mg twice daily for 10 days, cycled every 28 days as these patients could not be subjected for any intensive/ conventional chemotherapy due to poor performance status or co morbid conditions. Treatment-related toxicity was assessed after every cycle according to NCI-CTCAE criteria (version 4 .0).[8]

Assessment of response and clinical outcome: Response to treatment was assessed after every cycle of chemotherapy with RECIST criteria (version 1.0)[9] and clinical assessment. Response was also evaluated according to Ca125 levels.[10] Objective response rate (ORR) included complete and partial response. Progression-free (PFS) and overall survival (OS) were assessed.

Statistical analysis: PFS was defined as the time interval between start of oral cyclophosphamide, till the documentation of progressive disease. OS was defined as time between the date of start of treatment, till date of death or the date of last follow-up. PFS and OS were analysed by Kaplan meier survival analysis using IBM

SPSS 21.0. Chi square test was used to analyse the categorical variables.

Results

Out of 71 patients with mean age 61.2±0.74 years and mean Performance scale of 2 (ECOG), 62 patients (87.3%) had stage IIIC disease. Among them 44 patients (61.9%) were platinum refractory/resistant, while 26 patients (36.6%) were platinum sensitive; one patient had stage IV disease and because of her advanced age and poor performance status, she was considered for upfront oral cyclophosphamide. It was noted that 60 patients (84%) had received at least one line of previous chemotherapy before starting MOC, 43 patients (72%) had received two lines of chemotherapy prior to start of MOC. Majority were having abdominal disease (52.1%), whereas 28.2% of patients had both abdominal and visceral diseases at the start of metronomic therapy (Table 1).

Table 1: Patient characteristics

Variables	Cases (%) n= 71
Mean age	61.2±0.74 years
PS – ECOG	
1	11(15.4%)
2	42(59.1%)
3	18(25.3%)
Platinum sensitivity	
Refractory/resistant	44(61.9%)
Sensitive	26(36.6%)
No. of prior chemotherapy (n=60)	
1	11(18.3%)
2	43(71.7%)
3	6(10%)
Pattern of recurrence	
Abdominal diseases (peritoneal)	37(52.1%)
Visceral involvement	14(19.7%)
peritoneal + visceral involvement	20(28.2%)
CA 125 at baseline	
<35 IU/ml	3(4.2%)
>35 IU/ml	68(95.8%)
Serous	61 (85.9%)
Mucinous	3 (4.2%)
Clear cell	4 (5.6%)
Endometrioid	3(4.2%)
FIGO IIIC	62 (87.3%)
IV	9(12.7%)

The objective response rate (ORR) (complete and partial response) was 20%. There were two clinical CR documented; one patient had a vaginal vault only disease, whereas the other patient had only right sided malignant pleural effusion at the start of metronomic therapy.

The above mentioned complete responses in 2 patients belonged to platinum sensitive disease group and none among platinum resistant/ refractory group. ORR observed in 9 (34.6%) patients among platinum sensitive group and 5(11.3%) patients of platinum refractory/ resistant group, found to be statistically significant (p< 0.001). Median PFS in platinum sensitive group was 8 months where as it is 3 months in platinum refractory/ resistant disease.

Stable disease was seen in 22 patients (30.9%) and 17 patients had response duration ≥6 months, whereas 8 patients had continued response for more than 1 year. Among the study population, 49 patients (69.01%) progressed during treatment. Median PFS was 5 months (range 2 – 25 months), and the 12-month PFS rate was 11%; and the 12-month OS rate was 26%.(Fig. 1 & 2).

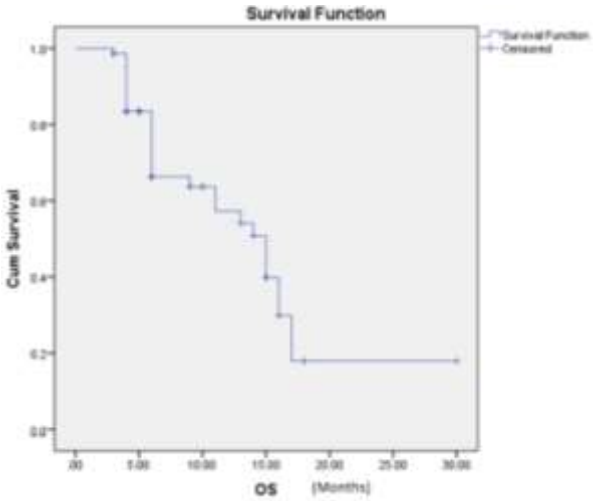

Fig. 1: Overall survival curve

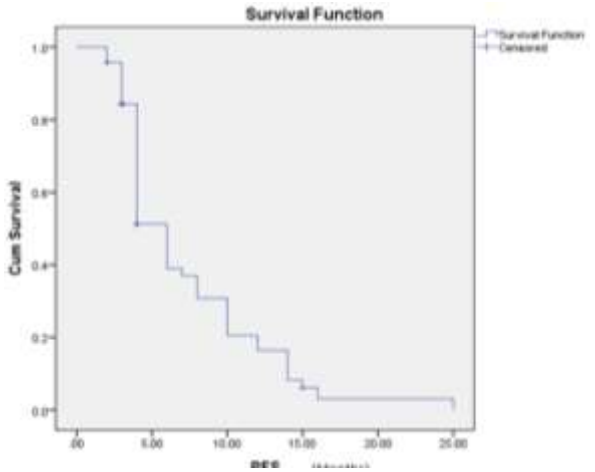

Fig. 2: PFS curve

Median PFS for patients who responded to MOC was 9 months where as it was only 2 months for those who did not (p = 0.01). Median OS was 14 months for responding patients whereas it was 8 months for patients progressed on MOC (p = 0.02) (Table 2).

Table 2: Survival results for responders to MOC and non-responders

	Responders (SD+PR) Months	Non-responders months	
Median PFS	9	2	P=0.012
Median OS	14	8	P=0.023

Out of 71 patients, 41 patients reported with various toxicities as shown (Fig. 3). Grade 2 nausea was seen in 4 patients, and 2 patient had grade 1 neutropenia.

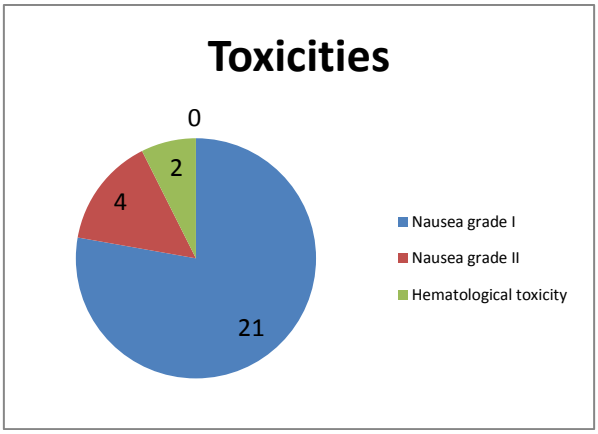

Fig. 3: Toxicities observed

Discussion

This is a retrospective analysis aimed at evaluating the efficacy of metronomic oral cyclophosphamide in recurrent and advanced ovarian cancer patients.

Table 3: Results of various metronomic studies in ovarian cancer

	No. of pts	Treatment	ORR
Beck(1965)[11]	126	CTX	48%
Handolias et al[12] (2016)	23	CTX	44%
Gabriella F[13](2014)	54	CTX	20.4%
In this study	71	CTX	20%

ORR in our series is 20% with oral cyclophosphamide. Interestingly it was noted that in platinum refractory ovarian cancer the ORR was 11%. This is a very powerful observation as it gives promising hope for patients with poor GC and in places where other standard chemotherapy cannot be considered.

Complete response was seen in 2 patients(3%). Partial response was seen in 12 patients (17%). Stable disease was seen in 22 patients, and 8 out of those 22 patients remained stable for more than a year. Various studies (Table 3) with cyclophosphamide has shown ORR from 20 -48%. Toxicities like grade 3 gastritis, grade 3 asthenia, and grade 3 neutropenia had been reported in some studies,[13] whereas in this study, oral cyclophosphamide was well tolerated, with no grade 3 or 4 toxicity.

In pre-treated recurrent Ovarian cancer, oral cyclophosphamide has provided median PFS and OS that were comparable to those achieved with other cytotoxic agents in retrospective as well as phase II studies.[13,15-17] Also patients responding to MOC experienced a very favourable PFS (mPFS = 9 months), and OS (mOS = 14 months) compared to non-responders (mPFS=2 months: mOS= 8 months) to cyclophosphamide.

In platinum sensitive recurrence, current standard of care will be rechallenging with platinum based regimens. Whereas in platinum refractory/ resistant diseases, non-platinum chemotherapies (taxanes, liposomal doxorubicin, topotecan, etoposide, gemcitabine, bevacizumab) are useful for salvage either as single agent or in combination.[18] But the usage of the above mentioned drugs/regimens are limited due to their toxicities in patients with poor performance status and co morbidities.

In this context, preclinical and clinical evidences have shown that metronomic cyclophosphamide used alone or in combination with other agents is able to induce antitumor T cell response by selectively reducing the circulating immunosuppressive T-regulatory cells and myeloid derived suppressor cells;[19-20] moreover, Metronomic oral cyclophosphamide has been also shown to inhibit cancer stem cells in vitro and in vivo,[21-22] thus suggesting that MOC could act as a multi-targeted approach.[23]

The recent data with metronomic oral cyclophosphamide[13] and our experience with intermittent low doses demonstrate that oral cyclophosphamide has significant activity in patients with recurrent ovarian cancer which is also well tolerated with negligible toxicity.

Conclusion

MOC is a valid option for heavily pre-treated recurrent ovarian cancer patients, especially with platinum refractory/ resistant disease who cannot be subjected to standard chemotherapy.

References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74-108.
2. Siegel R, Naishadham D, Jemal A: Cancer statistics. CA Cancer J Clin 2012,62(1):10–29.
3. Harter P, Hilpert F, Mahner S, Heitz F, Pfisterer J, Du Bois A: Systemic therapy in recurrent ovarian cancer: current treatment options and new drugs. Expert Rev Anticancer Ther 2010,10(1):81–88.
4. Basu P, De P, Mandal S, Ray K, Biswas J. Study of 'patterns of care' of ovarian cancer patients in a specialized cancer institute in Kolkata, eastern India. Indian J Cancer 2009;46:28-30.
5. Hanahan D, Bergers G, Bergsland E: Less is more, regularly: metronomic dosing of cytotoxic drugs can target

tumor angiogenesis in mice. J Clin Invest 2000,105(8):1045–1047.
6. Penel N, Adenis A, Bocci G: Cyclophosphamide-based metronomic chemotherapy: after 10 years of experience, where do we stand and where are we going? Crit Rev Oncol Hematol 2012,82(1):40–50.
7. Norrby K: Metronomic chemotherapy and anti-angiogenesis: can upgraded pre-clinical assays improve clinical trials aimed at controlling tumor growth? APMIS 2014,122(7):565–79.
8. Common terminology criteria for adverse events, version 4.0. Available in: http://www.hrc.govt.nz/sites/default/files/CTCAE%20manual%20-%20DMCC.pdf. last accessed on January 6th 2017.
9. Eisenhauer, E.A. et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer, Volume 45, Issue 2, 228–247.
10. Rustin GJ: Use of CA-125 to assess response to new agents in ovarian cancer trials. J Clin Oncol 2003, 21(Suppl. 19):187–193.
11. Beck RE, Boyes DA: Treatment of 126 cases of advanced ovarian carcinoma with cyclophosphamide. Can Med Assoc J 1968,98(11):539–541.
12. Handolias, D., Quinn, M., Foo, S., Mileshkin, L., Grant, P., Dutu, G. and Rischin, D. (2016), Oral cyclophosphamide in recurrent ovarian cancer. Asia-Pac J Clin Oncol, 12: e154–e160. doi:10.1111/ajco.12074.
13. Gabriella Ferrandina, Giacomo Corrado, Metronomic oral cyclophosphamide (MOC) in the salvage therapy of heavily treated recurrent ovarian cancer patients: a retrospective, multicenter study, BMC Cancer 2014, 14:947.
14. Ferrandina G, Paris I, Ludovisi M, D'Agostino G, Testa A, Lorusso D, Zanghi M, Pisconti S, Pezzella G, Adamo V, Breda E, Scambia G: Gemcitabine and liposomal doxorubicin in the salvage treatment of ovarian cancer: updated results and long-term survival. Gynecol Oncol 2005,98(2):267–273.
15. Watanabe Y, Koike E, Nakai H, Etoh T, Hoshiai H: Phase II study of single-agent gemcitabine in heavily pretreated Japanese patients with recurrent ovarian cancer. Int J Clin Oncol 2008,13(4):345–348.
16. Ferrandina G, Salutari V, Vincenzi B, Marinaccio M, Naglieri E, Loizzi V, Carpano S, Amadio G, Tonini G, Scambia G, Lorusso D: Trabectedin as single agent in the salvage treatment of heavily treated ovarian cancer patients: a retrospective, multicenter study. Gynecol Oncol 2013,130(3):505–510.
17. Safra T, Ron I, Boaz M, Brenner J, Grisaru D, Inbar M, Hayat H, Menczer J, Golan A, Levy T: Heavily pretreated ovarian cancer patients treated by single-agent gemcitabine. A retrospective outcome comparison between platinum-sensitive and platinum-resistant patients. Acta Oncol 2006,45(4):463–468.
18. J. A. Ledermann, F. A. Raja, C. Fotopoulou, A. Gonzalez-Martin, N. Colombo, C. Sessa, and on behalf of the ESMO guidelines Working Group, Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, Ann Oncol (2013) 24 (suppl 6): vi24-vi32 doi:10.1093/annonc/mdt.
19. Mikyšková R, Indrová M, Polláková V, Bieblová J, Símová J, Reiniš M: Cyclophosphamide-induced myeloid-derived suppressor cell population is immunosuppressive but not identical to myeloid-derived suppressor cells induced by growing TC-1 tumors. J Immunother 2012,35(5):374–384.
20. Folkins C, Man S, Xu P, Shaked Y, Hicklin DJ, Kerbel RS: Anticancer therapies combining antiangiogenic and tumor cell cytotoxic effects reduce the tumor stem-like cell fraction in glioma xenograft tumors. Cancer Res 2007,67(8):3560–3564.
21. Vives M, Ginestà MM, Gracova K, Graupera M, Casanovas O, Capellà G, Serrano T, Laquente B, Viñals F: Metronomic chemotherapy following the maximum tolerated dose is an effective anti-tumour therapy affecting angiogenesis, tumour dissemination and cancer stem cells. Int J Cancer 2013,133(10):2464–2472.
22. Andre' André N, Carré M, Pasquier E: Metronomics: towards personalized chemotherapy? Nat Rev Clin Oncol 2014,11(7):413–431.
23. Maiti R: Metronomic chemotherapy. J Pharmacol Pharmacother 2014,5(3):186–192.