Metronomic chemotherapy for pediatric refractory solid tumors: A retrospective single-center study

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Abstract

Background: Metronomic chemotherapy (MC) is based on chronic administration of chemotherapeutic agents at minimally toxic doses without prolonged drug-free breaks. MC has a multitargeted action of tumor angiogenesis inhibition and anticancer immune response stimulation and may also directly affect tumor cells to induce tumor dormancy. At our institute, MC has been introduced to treat patients with refractory/relapsed pediatric tumors. Methods: We retrospectively analyzed the data of pediatric patients with relapsed/refractory solid tumors who received treatment, including low-dose continuous administration of anti-cancer drugs. Results: Of the 18 patients, the disease statuses at the initiation of MC were complete remission ($n = 2$), partial remission/stable disease ($n = 5$), and progressive disease ($n = 11$). The overall survival rate was 61% at 12 months and 34% at 24 months, and the progression-free survival rate was 21% at 12 and 24 months. Eleven of 18 patients, with tumor stabilization or maintained remission/stable disease, showed certain advantages in terms of overall survival rate. Even if limited to progressive disease, the survival time of responders was prolonged compared to non-responders (median 19.4 months vs. 4.7 months, $P = 0.012$). Conclusion: Approximately half of the patients demonstrated temporal tumor stabilization and improved survival time, although most patients had progressive disease, and MC was administered as palliative therapy. Large-scale studies on pediatric MC are rare; however, previous reports and the present study support the conclusion that MC has the potential to play an important role in pediatric cancer treatment during the advanced stage, both in terms of prolonging life and maintaining quality of life.

Introduction

Over the past few decades, survival rates for pediatric cancer have markedly improved. However, certain high-risk or refractory/relapsed tumors show resistance to cytotoxic chemotherapy, resulting in a very poor prognosis. Moreover, conventional chemotherapy imposes side effects that limit dosing and impair quality of life (QOL). Angiogenesis, thought to be involved in all tissue growth, has gained the status of a key driver in the local and distant growth of cancer. Therefore, antiangiogenic therapy, an alternative approach to cancer treatment, is less likely to develop drug resistance.[1]

The term metronomic chemotherapy (MC), first coined by Hanahan in 2000, is defined as the continuous or frequent administration of chemotherapy at doses below the maximum tolerated dose without prolonged drug-free breaks.[2] In contrast to conventional chemotherapeutic regimens based on maximum-tolerated doses with periods for recovery, MCs mainly target endothelial cells within the tumor microenvironment and induce angiogenic dormancy in tumors.

One MC strategy is the combination of low-dose oral etoposide with or without differentiating and anti-angiogenic agents.[3,4]Another strategy is based on low-dose oral cyclophosphamide, sometimes combined

with weekly vinblastine, vincristine, and oral methotrexate.[5,6] In response to trial results, combination therapies named Combined Oral Metronomic Biodifferentiating Antiangiogenic Treatment (COMBAT), including etoposide and temozolomide or cyclophosphamide for relapsed pediatric solid tumors, have been published.[7,8] More recently, another combination therapy that included alternating 21-day cycles of low-dose oral cyclophosphamide and etoposide was developed.[9,10]These combination therapies also include antiangiogenic agents, such as retinoic acids, vitamin D3, thalidomide, celecoxib, fenofibrate, and bevacizumab.

Previous reports have shown that MC is an attractive option (i) as a palliative treatment for patients with measurable, resistant, progressive, and/or relapsed tumors, or (ii) as consolidation or maintenance therapy for patients with no measurable disease but with high-risk tumors, who are in first or second complete remission but have a very low probability of maintaining a long-term disease-free status.[4–13] In our institute, MC has been provided for patients with refractory/relapsed solid tumors.

Methods

Patient selection criteria and evaluation of responses

In this study, we defined MC as combination chemotherapy, including low-dose continuous oral cyclophosphamide 0.5–2.5 mg/kg/day or etoposide 10–50 mg/m^2/day.[4–10] We retrospectively investigated data of patients with solid tumors who experienced one or more relapse episodes or primary cases refractory to conventional chemotherapy. Of these refractory/relapsed cases, 18 patients received MC between 2012 and 2019 at our hospital.

All patients underwent regular imaging during MC, and their response to MC was assessed. Evaluation of response to MC was defined according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 as a complete response (CR) in the case of complete resolution of all demonstrable tumors; partial response (PR) in the case of 30% reduction in the longest diameter; stable disease (SD) in the case of $< 30\%$ decrease and $< 20\%$ increase in the product of diameters; and progressive disease (PD) in the case of 20% increase in the product of diameters.[14]

We defined responders as patients who received MC for at least 3 months and achieved CR or PR as the best response. The patients who remained with SD for at least 3 months, or the patients with progressive tumors that turned to SD that was maintained for at least 3 months after MC, were also classified as responders. Patients with tumors who received MC in PD status and continued progression during MC were defined as non-responders. If patients developed new areas of disease or showed disease-attributable clinical deterioration or death, or if the therapy was changed in spite of a less than 20% increase in tumor diameters, they were determined as progression and included as non-responders. The disease status at the start of MC was also defined following RECIST 1.1.

Overall, crude survival curves were constructed from the initiation of MC, including the period of survival after MC with other chemotherapy, radiation, or surgical treatment. To assess the tolerance of MC, we examined adverse events (AEs) and the incidence of febrile neutropenia (FN) according to Common Terminology Criteria for Adverse Events (CTCAE).[15] Monthly incidences of FN during MC were assessed in 9 of 18 patients with available clinical data and compared with those during conventional chemotherapy performed before the initiation of MC (median duration was 29.2 months, range 9.8–40.2 months).

2.Statistical procedures

Survival rates were computed based on Kaplan–Meier estimates of the survival function. Differences in survival rates were tested using the log-rank test for comparisons between two or more groups. Hazard ratio (HR) and 95% confidence interval (CI) were analyzed using Cox's proportional hazard models. The incidence of FN during MC or during previous periods of conventional chemotherapy was compared in 9 patients using Wilcoxon's signed-rank test. All statistical analyses were performed using EZR, which is a modified version of the R Commander utility designed to add statistical functions frequently used in biostatistics.[16] A p-value less than 0.05 was set to indicate statistical significance.

Results

1. Patient characteristics

Eighteen patients were enrolled with a median age at initiation of MC of 7.3 years (range, 2.7–16.1 years), and the sex ratio was 1:1. Seven patients were diagnosed with brain tumors, including 2 cases of atypical teratoid/rhabdoid tumor, 2 cases of ependymoma, and 1 case each of medulloblastoma, mixed germ cell tumor, and infantile hemispheric glioma. The remaining 11 tumors were 4 cases of neuroblastoma (NBL), 3 cases of rhabdomyosarcoma (RMS), and 1 case each of Ewing sarcoma, malignant peripheral nerve sheath tumor (MPNST), desmoplastic small round cell tumor, and extrarenal rhabdoid tumor.

The median time from diagnosis to MC initiation was 28 months (range, 14–84 months). The reasons for starting MC and disease status at that time were as follows: 2 patients with RMS and MPNST achieved CR and received MC as maintenance therapy; and 5 patients had PR to prior therapies or maintained SD without relapse (4 patients from this group received MC as consolidation therapy and the remaining patient with NBL received MC as a bridging therapy to 131-iodine-metaiodobenzylguanidine therapy). The remaining 11 patients received MC as palliative therapy for tumors that showed PD to conventional chemotherapies.

The choice of treatment regimen was at the discretion of the attending physician and was mainly set according to the newly published trials data available at the time.[4–10] Antiangiogenic agents, including bevacizumab, celecoxib, and fenofibrate, were combined when deemed appropriate. Two patients with RMS received a combination therapy of oral cyclophosphamide and intravenous vinorelbine, which was developed as maintenance therapy for primary RMS.[17]

Detailed characteristics of each patient are shown in Table 1. Of the 18 patients, 16 had received cyclophosphamide and 18 had received etoposide with a cytotoxic dose before MC—indicating no impact to the treatment outcomes of MC.

2. Clinical outcomes

The median observation time from the initiation of MC was 15.9 months (range, 1–102 months), and the median duration of MC was 7 months (range, 0–61 months). Figure 1 shows the clinical courses of individual patients. Patients 1 and 2 started MC as maintenance therapy after achieving CR and remained in CR after cessation of MC, with 6 and 102.3 months of progression-free survival (PFS) time. Among the 5 patients who started MC after achieving PR or SD after the initial cytotoxic chemotherapy, 1 patient remained in SD by MC for 20.3 months, and 3 patients experienced local relapse or PD after 3 to 9.5 months, respectively. One patient with residual bone marrow disease of NBL who achieved SD by MC for 3 months, was then bridged to 131I-metaiodobenzylguanidine therapy, which led to CR. Eleven patients started MC at the disease status of PD. Disease progression could not be controlled in 6 of these patients (54.5%), and they died from their disease. The remaining 5 patients achieved SD ($n = 4$) or PR ($n = 1$) at a median of 1.5 months (1–3.8 months); however, they experienced disease progression and eventually died.

Of the 16 patients who started MC at PR/SD/PD, 9 patients (56.3%) were classified as responders. Figure 2 shows the overall and progression-free survival curves, except for 2 patients who received MC as a maintenance therapy. The overall survival rate was 56.3% at 12 months and 27.3% at 24 months (Fig. 2A), and the median survival time was 14 months (range: 1–61.4 months). The PFS rate was 14.3% at both 12 and 24 months (Fig. 2B), and the median PFS time was 4.2 months (range, 3–102 months). Figure 3 shows the overall survival curves of the patients in response to the therapy. Responders, including PR, SD, and PD at the start of MC, had longer survival times than non-responders (median 21 months vs. 5.2 months; HR, 0.07; 95% CI, 0.014–0.38;$P < 0.01$; Fig. 3A). Although all patients with PD at the start of MC finally died within the observation period, the survival time of responders was significantly prolonged compared to non-responders (median 19.4 months vs. 4.7 months; HR, 0.15; 95% CI, 0.029–0.79; $P = 0.01$; Fig. 3B). Univariate analysis revealed that tumor pathogenesis, metronomic regimen, and combination therapy did not affect survival time (Table 2).

3. Adverse events and quality of life

The AEs observed during MC are shown in Table 3. Hematological toxicity was the most frequent AE, occurring in 15 of 18 patients, and 7 of the 15 patients required blood transfusion. FN occurred in 6 patients who developed grade 3–4 hematological toxicity. Other infections (aspiration pneumonia and *Herpes zoster*) were noted in 2 patients, respectively.

Fourteen patients received MC in outpatient settings, although they required long-term hospitalization before MC due to severe myelosuppression by cytotoxic chemotherapy. Six patients experienced AEs requiring hospitalization, with a median stay of 13 days.

Furthermore, we compared the incidence of FN and the number of blood transfusions in 9 patients with available detailed clinical records during cytotoxic chemotherapy before MC. The number of transfusions significantly decreased; median monthly incidence of transfusions were 0.83 during MC vs 0.0009 during chemotherapy before MC. Figure 4 shows the monthly incidence of FN during cytotoxic chemotherapy and MC; all patients, except for one, indicated an apparently decreased number of episodes. In terms of QOL, 10 out of 18 patients were of school age, and 5 (50%) of them continuously went to school while receiving MC, except while receiving cytotoxic chemotherapy. The remaining 8 patients were preschoolers, and 3 of them (38%) went to kindergarten or nursery school while receiving MC.

Discussion

Conventional cytotoxic chemotherapy has played an important role in the comprehensive treatment of cancer. However, it has limitations associated with side effects and requires long break periods, generally ranging from 2 to 3 weeks between treatment cycles, during which time tumors sometimes grow.[18] MC refers to the chronic administration of chemotherapeutic agents at relatively low, minimally toxic doses, without prolonged drug-free breaks.[1]

Here, we report the results of a single-center retrospective analysis of children with relapsed or refractory solid tumors who received a metronomic regimen based on low-dose continuous oral administration of anticancer drugs. In line with most published studies on pediatric MC, we have found benefits in terms of disease stabilization, defining "responders" as tumors that presented CR, PR, and SD.[8,10–12,14] The overall response rate was 61%, and 11 patients were defined as responders. Even among the patients who started MC in PD status, 45% presented with PR or SD.

Seven out of 11 responders turned to PD during MC, and 5 of them switched back to conventional chemotherapy. Of 5 responders who were in PD status at the start of MC, all died of the disease after tumor re-progression. However, the responders had prolonged survival times and maintained good QOL when compared to non-responders, with a median duration of response of 8 months (range, 3.3–102.3 months).

To date, most previous clinical trials and retrospective analyses of pediatric MC have focused on relapsed or refractory progressive tumors.[1,11] Although only a few cases achieved CR with MC, most reports indicate that some clinical benefit, including PR or SD, occurs in 25–67% of cases.

Robinson et al. performed a phase 2 trial on a metronomic 5-drug regimen including celecoxib, thalidomide, fenofibrate, and alternating 21-day cycles of etoposide and cyclophosphamide.[10] Of the 96 patients who were evaluated for tumor response, 1 achieved CR, 12 achieved PR, 36 achieved SD, and 46 showed PD; the response rate was 51% according to the same definition as in our study.

Zepletalova et al. reported the results of a prospective study for the COMBAT metronomic regimen that included low-dose daily temozolomide, etoposide, celecoxib, vitamin D, fenofibrate, and retinoic acid.[8] Of 62 patients with measurable disease, 40% improved and achieved remission or SD. The 2-year overall survival (OS) in all patients was 43.1%, which is statistically prolonged compared to historical controls (median OS was 15.4 months vs. 3.0 months). Our study suggested that MC can contribute to tumor dormancy and prolonged survival time, as expected from these previous larger-scale studies.

On the other hand, some clinical studies have reported discouraging data. For example, Pramanik et al., who performed a randomized control study (RCT) for altering oral etoposide and cyclophosphamide with

celecoxib and thalidomide, reported that 6-month PFS was not improved when compared to placebo.[12]

However, subgroup analyses revealed some encouraging results; patients who had received the drugs for at least 9 weeks without tumor progression had prolonged PFS. In other words, the initial treatment response after the start of MC is important for improving the prognosis. This is consistent with our analysis indicating that most of the responders showed radiographic response at the first imaging performed 1–3 months after the initiation of MC.

Because of the variety of patient backgrounds and previous treatments, it is difficult to discuss the tolerance of MC. However, our report has shown that MC is at least associated with fewer infectious episodes and transfusion dependence. In previous metronomic trials,[4–10] dosage regulation was permitted to reduce clinically significant toxicities or to avoid chemotherapy discontinuation. Most of our patients also received adjustment of oral dosage, and although hematological toxicity was almost inevitable, the episodes of FN in individual patients were significantly fewer when compared to conventional chemotherapy (Fig. 4: $P < 0.01$, paired t-test). This is considered an important advantage of MC because FN usually requires intravenous antibiotic treatment and hospitalization.

In Japan, cytotoxic chemotherapy is usually performed in the setting of continuous hospitalization in case of infection or the need for a blood transfusion. Consequently, pediatric patients spend less time with their families and hence sometimes experience loneliness. Moreover, if they are of school age, they have to give up their regular school life.[19,20] Treatment options on an outpatient basis are important for patients with a poor long-term prognosis.

In our retrospective analysis, AEs directly related to QOL, such as appetite for food, sense of fatigue, or performance status, were not evaluated sufficiently. However, MC can induce tumor dormancy without forcing hospitalization. Rather than simply seeking to prolong life, MC has the potential to provide a continuous treatment environment for the patient that prioritizes their life in the family and society.

Another expected role of MC is maintenance therapy.[13]In our study, two patients received MC in CR, and both patients completed the therapy without relapse and maintained CR. It is not clear whether the success of treatment in these two cases depended on MC. In the past, studies of MC limited to solid tumors in remission were rare. Senerchia et al. performed a controlled study on operated osteosarcomas comparing a regimen of methotrexate, anthracycline, cisplatin (MAP regimen), with MAP combined with MC, but no advantage was demonstrated in the combination therapy.[21] However, as mentioned later, patients with osteosarcomas are not suitable for verifying the advantage of MC.

Bisogno et al., in an RCT on children with RMS, reported that the addition of metronomic maintenance therapy with daily oral cyclophosphamide and weekly intravenous vinorelbine resulted in a significant increase in overall and event-free survival.[17] Although this trial was targeted to primary non-metastatic disease, efficacy in a palliative setting has also been reported.[22]

Focusing on adult oncology, MC as a maintenance therapy has been tried in various combinations, including for colorectal cancer, breast cancer, and ovarian cancer.[13] Although most of these studies are small, single-arm observations, a good safety profile and promising efficacy have been demonstrated. Of course, delayed complications (such as secondary malignancies due to long-term maintenance use of alkylators) should be considered,[23] and the appropriate treatment duration should also be discussed. Metronomic maintenance therapy for pediatric tumors requires further studies and accumulation of evidence, including treatment duration and delayed complications.

Recently, many molecular-targeted drugs have been developed that are becoming an important part of cancer treatment, either in combination therapy with anticancer drugs or as maintenance therapy. However, the identified actional mutations do not cover all cancers. Pediatric tumors, in particular, are known to have fewer target gene mutations than adult tumors.[24] MC may be a useful option as maintenance therapy for patients with cancers that are inappropriate for targeted agents.

This study has some limitations, as it was a small-scale, single-center retrospective analysis. The survival

time after MC initiation was not directly compared with that of conventional chemotherapy or no treatment. Moreover, tumor pathogenesis, primary site, clinical course, disease status before MC, combination therapy, and details of the metronomic regimen were variable. Although univariate analysis could not reveal significant confounding factors (expect for tumor response), there may have been a bias in the disease groups of the patients.

Previous studies have indicated that low-grade glioma, NBL, and RMS are likelier to respond to MC than high-grade glioma and osteosarcoma,[12,21,22,25] which could affect our response rate. It may be difficult to eliminate all of these limitations or to conduct comparative studies with a specific disease population, considering the rarity of pediatric cancer.

The literature on pediatric MC mostly includes case reports, retrospective analyses, and phase I and II clinical studies performed on heterogeneous populations. Our study, although even smaller with a more limited and variable patient population, demonstrated that MC can play an active role in palliative and maintenance therapy for relapsed or refractory pediatric solid tumors. These results are in line with the results of previous reports, and it would be worthwhile to accumulate experience and clinical data on MC for pediatric patients.

Conclusion

Our retrospective analysis suggested that MC demonstrated clinical benefits for relapsed or refractory pediatric cancers; about half of the progressive tumors presented tumor stabilization and prolonged survival time with higher QOL. The treatment was well tolerated in previously heavily treated patients, and the incidence of AEs decreased compared to conventional chemotherapy. Although large-scale analysis is lacking and many issues need to be resolved, MC can be an important part of cancer treatment.

Conflict of Interest statement

The authors have no conflicts of interest or source of funding directly relevant to the content of this article.

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Figure legends

FIGURE 1. Clinical course of individual patients from the initiation of metronomic chemotherapy. The interpretations of lines or symbols are indicated in the figure. Abbreviations; Pt: patient, DS: disease status, BR: best response, MC: metronomic chemotherapy, CR: complete response, PR: partial response, SD: stable disease, PD progressive disease.

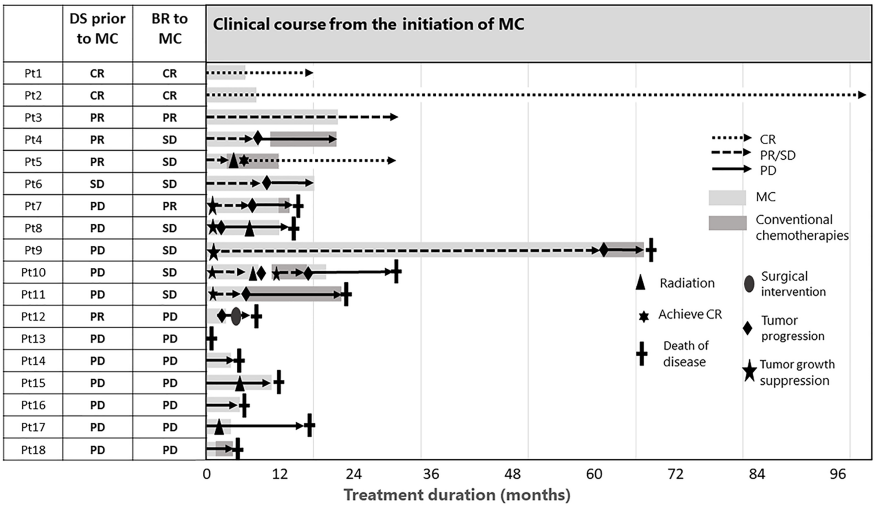
FIGURE 2 Survival curve of the patients after initiation of metronomic chemotherapy, except for 2 patients who received MC as a maintenance therapy. A: Overall survival curve; the overall survival rate was 56.3% at 12 months and 27.3% at 24 months. B: Progression free survival curve; the PFS rate was 14.3% at both 12 and 24 months. Abbreviations; MC: metronomic chemotherapy.

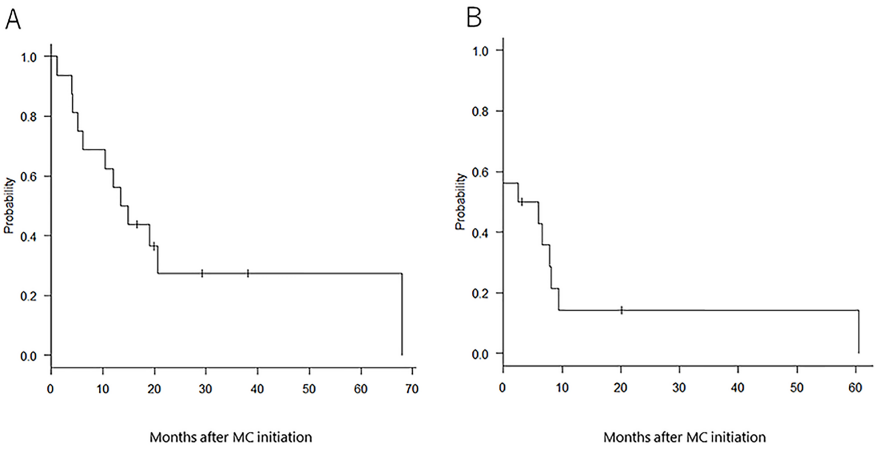
FIGURE 3. Overall survival curve by response to metronomic chemotherapy.

Panel A shows data of 16 patients; responders include patients with initially, partial remission, stable disease who keep disease status, and patients with progressive disease who achieved disease stabilization. The OS rate was 88.9% in responders and 14.3% in non-responders at 12 months; responders had longer survival

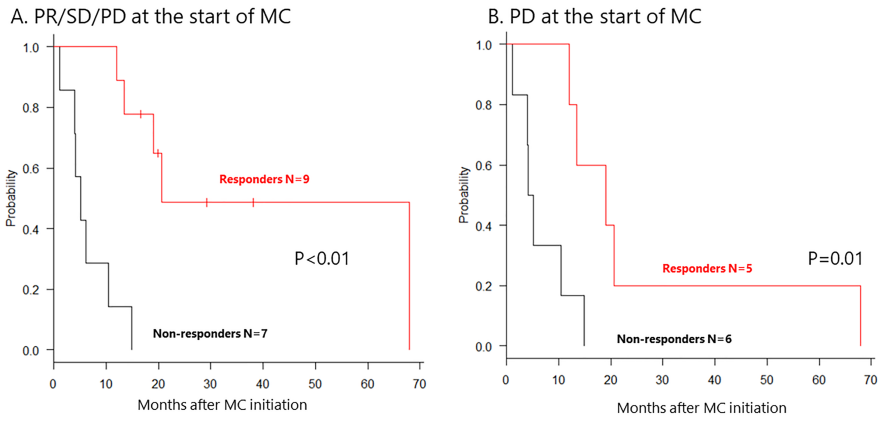
times than non-responders (median 21 months vs. 5.2 months). Panel B shows the data of patients who started metronomic chemotherapy in progression disease status. The OS rate was 80% in responders and 16.7% in non-responders at 12 months; responders had longer survival times than non-responders (median 19.4 months vs. 4.7 months). Abbreviations; MC: metronomic chemotherapy, CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease.

FIGURE 4 Incidence of febrile neutropenia per month during cytotoxic chemotherapy and metronomic chemotherapy. All patients, except for patient #14, indicated an apparently decreased number of episodes. Abbreviations; Pt: patient.

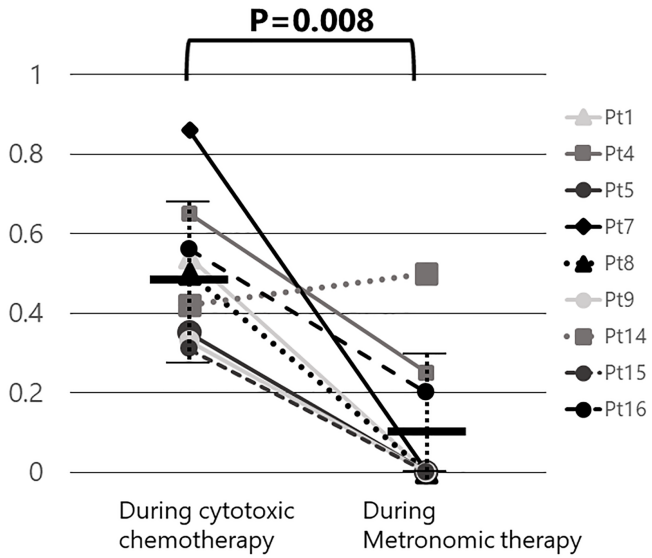




Overall survival curve (A) and Progression free survival curve (B) after initiation of MC



Overall survival curves by response to MC



Incidence of Febrile Neutropenia (per months)

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