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Low-grade serous ovarian cancer with *BRAF*^{V600E} mutation treated with metronomic chemotherapy — a case report and literature review

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ABSTRACT

Introduction. Ovarian cancer (OC) is the leading cause of cancer death worldwide. In Poland, it is the fourth leading cause of death from neoplasms in women. OC is a heterogeneous disease with low-grade cases characterized by a better prognosis, but poor chemosensitivity. Metronomic chemotherapy (MC) may be a beneficial approach.

Case presentation. We present a patient with low-grade serous ovarian cancer (LGSOC) with long-term disease control achieved with MC despite being resistant to standard-dose chemotherapy with paclitaxel and carboplatin. Overall survival (OS) of the patient was 65 months. MC was administered most of the time. The patient was treated with two metronomic regimens: topotecan plus cyclophosphamide and vinorelbine plus methotrexate, both in combination with hormone therapy. The cancer was found to harbor the *BRAF*^{V600E} mutation (v-raf murine sarcoma viral oncogene homolog B1, a valine-to-glutamic acid substitution at position 600), but that did not impact the treatment.

Conclusions. LGSOC has distinct features from high-grade serous ovarian cancer (HGSOC). MC may be a valuable option in LGSOC despite being understudied. The *BRAF*^{V600E} mutation occurs in 2–33% of low-grade serous ovarian tumors. It is a more common finding in LGSOC than in HGSOC. BRAF inhibition in OC may be a new therapeutic option. Some BRAF inhibitors have already been registered for solid tumors with this mutation.

Keywords: *BRAF*^{V600E} mutation, cyclophosphamide, ovarian cancer, low-dose metronomic chemotherapy, low-grade serous ovarian cancer, methotrexate, metronomic chemotherapy, topotecan, vinorelbine

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Introduction

Ovarian cancer (OC) accounted for 313 959 new cases and 207 252 deaths worldwide in 2020 [1]. In Poland, the standardized incidence rate is 15 cases per 100 000 inhabitants, making OC the fifth most common cancer in Polish women [2]. The death rate has

been declining in European countries [3]. In Polish women, OC is the fourth leading cause of cancer-related deaths [2]. OC is a very heterogeneous neoplasm [4]. Low-grade serous ovarian cancer (LGSOC) constitutes approximately 6% of ovarian neoplasms [5, 6] and has different biological characteristics [4], which results in distinct clinical management [7].

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Metronomic chemotherapy (MC) is an anticancer treatment based on the administration of cytotoxic agents more frequently and in lower doses compared to standard chemotherapy dosing. Metronomic administration uses different mechanisms of long-known chemotherapeutics. It is characterized by less toxicity than standard chemotherapy regimens. It is an option for patients with frailty syndrome and others who would not tolerate higher-dose chemotherapy [8, 9]. MC is especially useful in indolent cancers [10], including some cases of OC.

This case report presents a patient with LGSOC who was successfully treated with MC for several years.

Case report

A 57-year-old female was diagnosed with a borderline tumor (BT) of the left ovary in November 2005. Her family history was non-significant for cancer, and germline *BRCA* (breast cancer) mutations were excluded. The patient underwent hysterectomy and bilateral adnexectomy. No additional treatments were administered at that time.

The patient remained disease-free for a decade. In July 2016, cancer recurred in the pelvis and abdomen. The International Federation of Gynecology and Obstetrics (FIGO) system stage IV was established. The patient underwent an operation, during which cytoreduction was performed. The surgery was not radical due to massive dissemination. Postoperative histopathological examination revealed LGSOC. The histopathological samples from primary surgery were inaccessible; therefore, it was not possible to verify, considering the new criteria, whether the cancer initially diagnosed was, in fact, LGSOC.

In August 2016, adjuvant chemotherapy based on paclitaxel and carboplatin was initiated; chemotherapy was administered at three-week intervals. After 5 cycles, disease progression was diagnosed due to the appearance of a lesion in the vaginal fornix. In December 2016, hormone therapy (HT) with tamoxifen was started, but at that time the status of hormone receptors (HRs) was not determined.

In February 2017, symptoms of intermittent gastrointestinal obstruction developed due to infiltration of the intestinal loop by newly discovered epigastric implants. The level of CA-125 (cancer antigen 125) also increased. It was decided to discontinue tamoxifen and start next-line chemotherapy. Considering the patient's good general condition and lack of cancer symptoms, it was decided, in consultation with the patient, to use MC instead of standard-dose chemotherapy. In the opinion of the attending physician, the selected therapeutic option was optimal to achieve disease control and maintain the patient's high quality of life (QoL).

From February 2017 to June 2018, the patient was treated with oral topotecan in a metronomic manner (1 mg per day for three days and one day off) and cyclophosphamide (50 mg per day). From July 2017, due to episodes of neutropenia, the dose of topotecan was reduced (1 mg every other day). During further treatment, the dose of topotecan had to be increased again due to the increase in CA-125 (1 mg per day for two days and one day off), but it resulted in recurring episodes of leukopenia. The patient reported general weakness and abdominal pain during therapy. The overall tolerance to treatment was good. Radiological evaluation after 3 months of MC showed stable disease.

In May 2018, the status of HRs was determined in the second surgical sample. The expression of the estrogen receptor (ER) was 90%, and there was no expression of the progesterone or androgen receptors. Tamoxifen was added to the treatment due to the positive ER status, but increasing CA-125 levels were found, and it was replaced with letrozole. This combination of MC and HT was maintained until February 2019.

In February 2019, due to cancer progression, topotecan and cyclophosphamide were replaced with another metronomic combination: vinorelbine (50 mg three times a week) and methotrexate (5 mg twice a week). Letrozole was discontinued. Side effects included pain in the abdomen and spine, especially on days of methotrexate administration. In January 2020, tamoxifen was reintroduced. The patient remained in triple treatment (vinorelbine, methotrexate, tamoxifen) until October 2020. In October 2020, tamoxifen was replaced again with letrozole due to biochemical (CA-125) progression.

In December 2020, the patient participated in molecular screening as part of the RAGNAR clinical trial, evaluating erdafitinib therapy in advanced solid tumors with the activating mutation of the presence of the FGFR (fibroblast growth factor receptor) (NCT04083976). The patient was diagnosed with the *BRAF*^{V600E} mutation, which made her ineligible for this clinical trial.

In April 2021, a decision was made to discontinue vinorelbine, methotrexate, and letrozole due to evident clinical, biochemical, and imaging progression as well as the lack of perspective for further benefit from this treatment. Pegylated liposomal doxorubicin administered at 2-week intervals was introduced. In June 2021 the regimen was intensified by adding oral cyclophosphamide daily. This treatment was terminated in August 2021 due to progression and poor tolerance. Carboplatin and paclitaxel administered at weekly intervals were introduced and maintained for 8 weeks. Meanwhile, an immunohistochemical test was also performed using available paraffin blocks from the second surgery: cancer cells expressed WT1 (Wilms tumor 1) and PAX8 (paired box 8), and the status of HER2 (human epidermal growth factor receptor 2) was negative (1+). The proliferative activity of Ki67 was 12%.

At the turn of October and November 2021, the patient suffered from COVID-19 pneumonitis and was, therefore, hospitalized in the infectious diseases ward. The SARS-CoV-2 infection was complicated by bacterial superinfection. Due to poor general condition, the patient was disqualified from anticancer treatment and refused further diagnostic and therapeutic procedures, except for analgesic treatment. The patient died in the second half of December 2021 at the age of 72, having lived 65 months since the diagnosis of metastatic cancer.

Discussion

This case report is notable for OS of the patient who was treated most of the time with MC. The patient lived for 65 months after the diagnosis of metastatic OC although survival from the first diagnosis was much longer.

There is controversy surrounding the natural history of low-grade and borderline ovarian tumors. Some authors believe that LGSOC is mainly a recurrent BT [7]. The presented case seems to follow this pattern although it must be noted that initial pathological samples were not available for re-verification after recurrence.

The patient's cancer had indolent biology, which partially explains long OS [11]. In the article by Gockley et al. [12], median OS for patients with low-grade stage IV OC was 55.2 months. In a study by di Lorenzo et al. [13], median OS of patients with low-grade OC who received suboptimal cytoreduction was 35.2 months, and the article by Grabowski et al. [14] reported OS of 35.0 months.

At the time of recurrence, the patient underwent cytoreductive surgery, followed by adjuvant chemotherapy with paclitaxel and carboplatin. This treatment is considered standard in this clinical setting [15–17]. However, the patient experienced progression on the first-line regimen. Primary platinum resistance is a recognized negative prognostic factor [18].

High chemoresistance is typical for tumors with a low histopathological grade [19]. In slow-proliferating tumors, cell division occurs less frequently than in tumors with a high proliferation rate. Chemotherapy administered according to the maximum-tolerated-dose paradigm targets mainly cells that are actively dividing and not cells in the G0 phase. This makes slow-proliferating tumors less susceptible to chemotherapy. The use of cytotoxic agents in maximal doses at longer intervals between treatment cycles allows for the regeneration of healthy body cells. In slow-proliferating cancers, the continuous use of lower doses of cytotoxic agents seems to be a more reasonable approach because it inhibits cell division as soon as it occurs [20].

In the case of the presented patient, MC was chosen as an appropriate treatment option for low-grade cancer. MC is defined as the continuous administration of cytotoxic agents in low doses. It differs in effect from standard chemotherapy regimens, in which maximal doses of drugs are used in a short period followed by a break to allow regeneration. Long-term disease control remains a priority in MC [21], while standard chemotherapy intends to obtain an objective response. This divergence in objectives is particularly visible in advanced OC, where MC is administered without interruptions, and standard chemotherapy after achieving remission is discontinued until the next recurrence. In highly differentiated OC, it seems more beneficial to use the cytostatic effect of the metronomic approach than the cytotoxic effect of the maximum dose approach [22]. In addition, antiangiogenic properties as well as immune system stimulation and impact on tumor microenvironment are also emphasized in MC [23]. Given all the potential advantages of MC, there is surprisingly little scientific research on this topic. The available evidence comes mainly from observational studies and the experience of individual cancer centers. The optimal drug combinations for MC remain largely unknown [24], and prospective randomized trials comparing MC with standard chemotherapy in OC are lacking.

The described patient received topotecan and cyclophosphamide as the first metronomic regimen. The only work that addresses this combination is a retrospective analysis by Wysocki et al. [25]. In that study, the objective response rate (ORR) was 27.2%, and the disease control rate (DCR) was 86.3%. Median progression-free survival (PFS) at 3, 6, and 12 months was 57.2%, 26.7%, and 11.3%, respectively, which is comparable to the results achieved by classical fractionation of topotecan. The biochemical response to MC was shown to be the most important predictor of improved PFS. The combination of topotecan and cyclophosphamide was well tolerated. No patient was forced to discontinue treatment due to toxicity. The most common adverse reaction was anemia. In addition to myelotoxicity, hepatic and renal damage (mainly low-grade) was also observed in patients [25]. The presented patient received daily oral topotecan, which is less toxic than when administered intravenously in cycles lasting several weeks despite the similar overall dose [26, 27].

As a second regimen of MC, the patient received methotrexate and vinorelbine; drugs with a different mechanism of action from topotecan and cyclophosphamide administered previously. There are no reports in the literature on the combined use of methotrexate and vinorelbine as MC in OC. However, both drugs are used in a metronomic manner.

Methotrexate has been reported in combination with cyclophosphamide as maintenance MC in advanced OC after achieving a complete response on a platinum-paclitaxel regimen. Compared to the untreated control group, patients receiving this maintenance MC benefited from 2.5 months longer PFS [28]. The combination of methotrexate and cyclophosphamide as MC has also been described in several other cancers, including advanced breast cancer. The study by Lu et al. showed an ORR of 3.8%, but a DCR of 41.4% [29], which illustrates the mentioned-above clinical effect of MC, which is prioritizing disease control over eradication [30, 31].

In the literature, metronomic dosing vinorelbine is used most often in the treatment of non-small-cell lung cancer (NSCLC) and advanced breast cancer. As a drug that inhibits formation of microtubules and, at higher concentrations, also damages them, vinorelbine inhibits the transport of the ER complex and thus has the potential to be effective in ER-expressing OC, as in the described patient. Metronomic vinorelbine was compared in a phase II randomized trial with the best supportive care in patients with advanced NSCLC. The vinorelbine group had a significantly lower median progression follow-up rate ($p = 0.049$) and 1.5 month longer PFS. OS, ORR, and QoL were not significantly different between the two groups. The high percentage (25%) of discontinuation of treatment due to toxicity (mainly neutropenia) was surprising to researchers [32]. A 2020 meta-analysis evaluating metronomically administered vinorelbine in stage IIIB/IV NSCLC cancer showed an ORR and a DCR of 12% and 48%, respectively. Median PFS was 3.46 months and OS was 8.22 months. The most common serious adverse reaction was neutropenia. The conclusions emphasized that MC is a convenient and cost-effective form of treatment suitable for elderly patients with frailty syndrome [33].

Hormone therapy is not as effective in OC as in “classical” hormone-sensitive neoplasms, such as breast or prostate cancers. The literature indicates that the expression of female HRs in OC is a predictive factor for HT. It should be noted that LGSOC mostly has a high expression of HRs [34]. Randomized trials, which evaluated HT in OC as an alternative to chemotherapy or as a maintenance treatment, have not been positive so far [16]. Letrozole is currently being studied in low-grade ovarian tumors (NCT05601700). Combining HT with MC is justified because both forms of treatment have cytostatic properties, leading to a synergistic effect [35].

The *BRAF* mutation plays an important role in the carcinogenesis of melanoma, colorectal cancer, NSCLC, and other tumors [36]. The *BRAF* gene is a proto-oncogene that encodes a serine-threonine kinase that transmits a signal from the growth factor receptors. The activating mutation in this gene is responsible for strong stimulation of the mitogen-activated protein kinase (MAPK) pathway. This results in increased proliferation

and angiogenesis, which are key elements of carcinogenesis. The reported frequency of *BRAF* mutations is highest in melanoma (50% of cases) with a much lower incidence in other malignancies, where it typically coexists with different driver alterations [37, 38]. The mutation rate in LGSOC varies from 2% to 33% [39]. The literature emphasizes that mutations in the MAPK pathway are rarer than in high-grade serous ovarian cancer [40]. Sometimes, paradoxically, it is also associated with a positive prognosis. In LGSOC, mutation has been shown to be associated with early disease diagnosis, no need for chemotherapy treatment, and longer OS [40]. Inhibition of *BRAF* in low-grade OC has been investigated in several trials. In cohort H of the NCI-MATCH study, sixteen different tumor types harboring the *BRAF*^{V600E} mutation were treated with a combination of dabrafenib and trametinib. LGSOC was one of the most common histology types (5 cases). Four patients achieved a partial response, and one patient had stable disease [41]. ROAR was a similar study but did not include low-grade serous ovarian tumors [42]. The TAPUR study analyzed six patients with OC treated with a combination of vemurafenib and cobimetinib. Three had an objective response, and one had a complete response [43]. In June 2022, the Food and Drug Administration approved the combination of dabrafenib and trametinib for solid tumors with *BRAF* mutations based on the NCI-MATCH [41] and ROAR [42] studies. This means that if the patient was alive today, she could potentially be treated with dabrafenib and trametinib as tissue-agnostic targeted therapy.

Conclusions

The patient presented achieved satisfactory OS despite platinum resistance. Her 65-month OS exceeded OS medians in LGSOC reported in the literature. MC has promising activity and a manageable toxicity profile. It works well in slowly proliferating and relatively chemoresistant tumors, including LGSOC. MC has a synergistic effect with HT. Both methods could be combined. Metronomic regimens deserve evaluation in prospective trials. Currently, there is little high-quality evidence about MC. *BRAF*^{V600E} constitutes a new molecular target in OC, especially in low-grade tumors. Some *BRAF* inhibitors have already been available as tumor-agnostic therapy. They potentially will support chemotherapy, including MC.

Article Information and Declarations

Ethics statement

Article have been conducted according to the principles stated in the Declaration of Helsinki.

Author contributions

M.R.-S.: methodology, writing — original draft preparation; P.M.: methodology, writing — original draft preparation; Ł.K.: formal analysis, investigation, writing — review & editing; M.Ł.: investigation, writing — review & editing; P.M.P.: conceptualization, methodology, formal analysis, writing — original draft preparation, writing — review & editing, supervision.

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Conflict of interest

The authors declare no conflicts of interest.

Supplementary material

None.

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