

Oral metronomic cyclophosphamide in advanced ovarian cancer: long-lasting clinical response in an elderly frailty patient

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Elderly patients with ovarian cancer are an increasing population and many of them are frailty with an increased risk of postoperative complications, chemotherapy intolerance and mortality. Metronomic chemotherapy is the chronic administration of low, equally spaced, doses of antineoplastic drugs with therapeutic efficacy and low toxicity. Oral metronomic cyclophosphamide has gained increasing interest in recent years in the treatment of patients with recurrent ovarian cancer. We report the case of a 87-year-old and -frailty woman with advanced ovarian cancer, not eligible for surgery or standard first-line intravenous chemotherapy. The patient has received oral metronomic cyclophosphamide with a long-lasting clinical response and improved performance status. Oral

metronomic cyclophosphamide is a promising treatment for elderly and frailty advanced ovarian cancer patients and should be further investigated. *Anti-Cancer Drugs* 30:964–968 Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.

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Introduction

Elderly patients affected by gynecological cancers are rising because the progressive demographic changes resulting in a larger geriatric population. Ovarian cancer is common in the elderly and its incidence increases with age to reach a peak during the seventh decade of life [1].

Standard first-line treatment of ovarian cancer consists in optimal debulking surgery followed by intravenous chemotherapy with a combination of carboplatin and paclitaxel [2].

In choosing a treatment, we have to consider a lot of patient-related factors, such as performance status, comorbidities and compliance to treatment. The higher incidence of comorbidities in elderly patients can increase the risk of treatment-related toxicities. Elderly women, particularly those with high comorbidities and obvious unresectable disease, are at the highest risk of surgical morbidity. The major side effects of chemotherapy, such as myelosuppression and specific organ or tissue toxicities, are frequently too severe in elderly population, leading to delays in schedule administration, dose reductions or discontinuations with suboptimal results.

The division of elderly patients into young old (65–75 years), old (76–85 years) versus the oldest people (more than 85 years) could be useful because it is associated with a greater prevalence of comorbidity and a functional

dependency [3]. Nevertheless, an assessment of purely chronological age could be misleading, much more important is the biological age. Frailty is an emergent concept and also its assumption based on age alone may lead to inadequate and inappropriate treatments. Comprehensive Geriatric Assessment is recommended, but it is time-consuming. Some authors have proposed screening tools that can be used to rapidly identify frailty patients. In our experience Vulnerable Elders Survey – 13 (VES-13) and modified Frailty Index (mFI) are valuable tools [4,5].

In elderly patients, several strategies have been described to improve feasibility and tolerability while maintaining efficacy of the first-line treatment, including single-agent therapy, weekly schedules and baseline dose reductions. Another strategy could be the oral administration of some antineoplastic drugs, such as cyclophosphamide, an alkylating agent widely used in the first-line treatment of ovarian cancer before the taxane era [6].

Metronomic chemotherapy is the chronic administration of low, equally spaced, doses of antineoplastic drugs with therapeutic efficacy and low toxicity. Oral metronomic cyclophosphamide has gained increasing interest in recent years as a promising therapy in patients with recurrent ovarian cancer after previous multiple lines of chemotherapy [7–10].

We report the case of an elderly and frailty patient with advanced ovarian cancer, not eligible for surgery

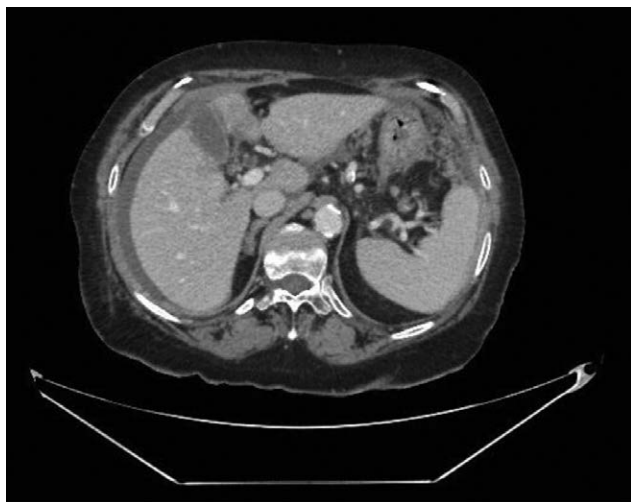
or standard first-line intravenous chemotherapy, with a long-lasting clinical response to oral metronomic cyclophosphamide.

Case presentation

In April 2017, a 87-year-old woman was admitted at the Emergency Department of Mauriziano Hospital in Torino because of abdominal pain and emesis. She was nulliparous, in menopause since she was 54 and did not receive hormonal replacement treatment. The relevant previous medical history consisted of permanent atrial fibrillation, hypertension, peripheral vascular disease, dyslipidemia, chronic obstructive pulmonary disease, hiatal hernia with erosive gastritis and iron deficiency anemia. Furthermore, the woman presented a history of renal tuberculosis with consequent unilateral nephrectomy and she had a pulmonary embolism in 2009. She was taking a lot of drugs: bisoprolol, furosemide, spironolactone, losartan, gastric protector, benzodiazepine, antidepressant and rivaroxaban, an oral anticoagulant. She had no family history of breast and ovarian cancer.

The level of Ca125 was high (543 UI/ml). Ultrasound scan showed in the right adnexal region a solid mass of 60 mm × 40 mm adherent to the sigma and in the left adnexal region a similar solid mass in close association with rectum and uterus. A computed tomography (CT) scan evaluation confirmed the two tumor lesions in the adnexal sites and revealed ascites, omental cake, diffuse peritoneal and diaphragmatic carcinomatosis with two lesions (15 and 36 mm diameter) on the glissonian capsule (Fig. 1); para-aortic lymphadenopathy was also reported. At cytohistological examination on ascites and a peritoneal node, ovarian serous adenocarcinoma was diagnosed.

Fig. 1



CT abdomen before starting treatment with metronomic cyclophosphamide (April 2017). CT, computed tomography.

Two questionnaires for assessment of frailty, VES-13 and mFI, were administered. Both VES-13 and mFI showed a state of frailty: VES-13 value was 5 and mFI was 4 (Tables 1 and 2). Due to the frailty condition, the abnormal renal function and the extension of the disease, the patient was not eligible for surgery or standard first-line chemotherapy with carboplatin and paclitaxel.

The patient wish was also assessed: in her capacity as a retired midwife, she well knew the disease and refused any surgical or endovenous medical treatment. The possibility of palliative hormonal therapy or metronomic chemotherapy was discussed with the patient and her family: the second option was chosen. In May 2017, oral metronomic chemotherapy was started, the regimen was low-dose cyclophosphamide (50 mg) every day.

In July 2017, after 2 months of treatment, Ca125 level decreased to the normal range (28 UI/ml). In October 2017, after 5 months of treatment, Ca125 level was 12.2 UI/ml. A CT scan evaluation of chest and abdomen revealed a significant reduction of the peritoneal and diaphragmatic carcinomatosis with disappearance of the ascites (Fig. 2); the two solid adnexal lesions were both reduced in size as well as the lymphadenopathy.

Table 1 Items evaluated in Vulnerable Elders Survey – 13

Element of assessment	Score
Age (years)	
75–84	1
≥85	3
Self-reported health	
Good or excellent	0
Fair or poor	1
ADLs/IADLs	
Needs helps in	
Shopping	1
Managing money	1
Doing light housework	1
Transferring	1
Bathing	1
Activities	
Needs help in	
Stopping, crouching, or kneeling	1
Lifting or carrying 5 kg	1
Writing or handling small objects	1
Reaching or extending arms above shoulders	1
Walking 500 m	1
Doing heavy houseworks	1

ADL, activities of daily living; IADL, instrumental activities of daily living.

Table 2 Eleven items of the modified Frailty Index

	Items
1	Diabetes mellitus
2	Functional status
3	Respiratory problems
4	Congestive heart failure
5	Myocardial infarction
6	Other cardiac problems
7	Hypertension
8	Peripheral vascular disease
9	Impaired sensorium
10	Cerebrovascular disease
11	Cerebrovascular disease with neurological deficit

Fig. 2



CT abdomen after 5 months of treatment with metronomic cyclophosphamide (October 2017). CT, computed tomography.

In December 2017, the patient fell down at home and had a femoral head fracture. Because of age and comorbidities surgery was not performed, so since this moment she is mainly in bed, but she feeds, intestinal function and diuresis are regular.

The patient continued oral metronomic cyclophosphamide. The treatment was well tolerated without any dose reduction or discontinuation. The only reported side effect was grade 1 fatigue.

Due to the difficult mobilization, the course of the disease has been monitored monthly with blood exams, Ca125 dosage and assessment of general conditions. Blood exams were in the normal ranges. The Ca125 value was stable around 14 UI/ml. General condition was stable.

In December 2018, after 19 months of treatment, a subcutaneous nodule raised in the lower-left quadrant of the abdomen. The Ca125 level was 19 UI/ml in November 2018, 16 UI/ml in December and 16 UI/ml in January 2019. A CT scan assessment performed on 25 January 2019 reported a further decrease of the omental cake, but an increase in peritoneal carcinomatosis with the appearance of a cystic mass in the lower-left quadrant of the abdomen; the adnexal lesions and the para-aortic lymphadenopathy were stable, while 2 cm lymphadenopathies appeared at hepatic hilum; no ascites has been found. Blood exams are still in the normal ranges, but pulmonary function is deteriorated. At the beginning of February, metronomic cyclophosphamide has been stopped and palliative treatment with an aromatase inhibitor has been started.

Discussion

The article reports an oldest-old (87 years) ovarian cancer patients with several comorbidities who had 19 months

of response – clinical benefit with oral metronomic cyclophosphamide.

The patient was not eligible for surgery neither for intravenous chemotherapy with carboplatin and paclitaxel because her functional status and comorbidities made her a frailty subject. Frailty is a state of vulnerability to poor resolution of homeostasis following a stress because of the cumulative decline in multiple physiological systems [11]. Surgery and chemotherapy are stressor events. Chronological age is a poor indicator of frailty and cannot predict well surgery complications and toxicity of chemotherapy. We use two tools to rapidly identify this condition: VES-13 and mFI.

VES-13 is a simple function-based frailty screening tool that can be administered within 5 minutes. It was developed in 2001 to identify older people at risk for health deterioration. Although VES-13 was not originally designed to answer specific oncological questions, it has been studied as a screening tool in oncology in several studies [12,13]. The score ranges from 0 to 10 and a score ≥ 3 identify vulnerable subjects [5].

Another screening tool is mFI, which utilizes 11 National Surgical Quality Improvement Program variables derived from the Canadian Study of Health and Aging Frailty Index and has been validated in several surgical specialties. mFI is more focused on comorbidities, and in the literature, it was applied to identify patients at high risk for severe surgical complications, also in gynecology oncology [14,15]. A mFI score is calculated by adding the number of variables; patients with a score of 4 or greater are considered frailty.

Our patients were frailty at the assessment with both the screening tools. In frailty patients, it could be difficult to choose the most appropriate treatment because they are underrepresented in clinical trial and consequently data on surgery complications or expected side effects of chemotherapy in the elderly are often inadequate [16]. Elderly population is more likely to experience reduction of delivered dose intensity and delays in chemotherapy administration. The literature demonstrates that delays are associated with worsened overall survival (OS) in elderly oncologic patients and that hematological toxicity is a common reason for the delay. Indeed, aging is associated with decrease bone marrow reserve and an increased risk of myelosuppressive-associated complications due to chemotherapy [17,18]. An alternative strategy in order to avoid toxicity and delays could be the chronic administration of low doses of chemotherapeutic drugs. The use of regimens that involve the frequent, even daily, administration of small doses of drugs without prolonged drug-free breaks has been termed ‘metronomic’ chemotherapy. It allows chronic treatment with therapeutic efficacy and low toxicity and it has been demonstrated to be effective in several types of tumors (breast, sarcoma, lung and prostate) [19].

Intravenous cyclophosphamide, an alkylating agent, was a milestone in the past for the treatment of ovarian cancer. Then, clinical trials demonstrated that intravenous combination of paclitaxel and carboplatin gives a longer OS in patients with optimal cytoreductive surgery and this combination replaced intravenous cyclophosphamide [20].

Metronomic oral cyclophosphamide has gained interest in recent years as a promising treatment of recurrent ovarian cancer, also in heavily pretreated patients [8–10].

The efficacy of metronomic cyclophosphamide can be explained by an antiangiogenic effect that continuously inhibits endothelial cells attempting to restore the vascular status of the tumor. Intratumoral vascular endothelial cells proliferate rapidly and are vulnerable to cytotoxic agents. However, the long interval between cycles of conventional chemotherapy allows the survival and regrowth of a small number of endothelial cells, permitting tumor angiogenesis to persist. Continuous, low-dose chemotherapy, on the other hand, enhances the antiangiogenic effect and may also enhance a proapoptotic effect in both dividing tumor cells and endothelial cells. The induction of thrombospondin-1, an endogenous inhibitor of angiogenesis, seems to be the leading mechanism. In addition, the mobilization, viability and levels of angiogenesis may be strongly suppressed by metronomic chemotherapy. Previous studies described a direct effect on the induction of tumor stem cell differentiation, with a reduction in circulating regulatory T cells leading to a stimulation of antitumor T-cell response [21–23].

Main known cyclophosphamide side effects are cytopenia, hemorrhagic cystitis and cardiac toxicity, but they occur when using high dose of drug. As also reported in the retrospective multicentric study by Ferrandina *et al.* [8], low-dose cyclophosphamide has a good toxicity profile; in this study, they reported just one case of grade 3 anemia, one of grade 2 nausea/vomiting and grade 3 asthenia, one patient with grade 1 cutaneous toxicity, one case of pruritus grade 1 and just one case of discontinuation therapy due to grade 3 gastritis, on a total of 370 evaluated courses. In our case, the patient only presented a grade 1 fatigue. This regimen can be administered in outpatient setting and this can be a key point for elderly frailty people with walking and mobilization difficulty, such as our patient. Last, the costs of oral metronomic cyclophosphamide are significantly lower than the costs of intravenous cytotoxic drugs. The antiangiogenic effects of metronomic cyclophosphamide, as described in some case reports and one retrospective review, suggest that adding bevacizumab in heavily pretreated patients with recurrent ovarian cancer improves progression free survival and OS in responders. However, data about adverse events and cost-effective ratio are not totally clear. Hence, well-designed clinical trials are needed to evaluate this association [24]. Another emergent interesting association is with poly ADP ribose polymerase inhibitors. Kammar *et al.* [25] demonstrated

in a small randomized trial of oral cyclophosphamide with or without velaparib that the addition of velaparib did not increase the response rate.

Conclusion

Ovarian cancer in elderly people represents a challenge for gynecological oncologists, in part for the increase in incidence in advanced age and also because of the lack of guidelines and standard treatment in this category of patients. It is important to assess frailty status of patients before deciding the best therapeutic option and starting treatment. Age alone is an inappropriate parameter to define the frailty condition. For our patient treatment with low-dose continuous cyclophosphamide led to a clinical response with a low toxicity profile and without affecting quality of life. Metronomic cyclophosphamide could be a feasible treatment option for ovarian cancer patients not eligible for surgery or standard intravenous platinum-based chemotherapy because of age, comorbidities and poor functional status.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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