



Case Report

# Metronomic Chemotherapy is an Effective and Well Tolerated Treatment in Advanced Triple Negative Breast Cancer Patients: A Case Report of a Very Long Responder and Literature Review

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## Abstract

Triple negative breast cancer (TNBC) represents a heterogeneous entity characterized by aggressive clinical course, early recurrence and relatively poor survival in advanced stages. Currently available chemotherapy regimens are generally associated with unfavourable adverse events (Aes) that can lead to treatment discontinuation, mostly in frail patients (such as older patients). In this complex scenario, metronomic chemotherapy is acquiring an increasingly important role thanks to its effectiveness and its manageable safety profile. Although median survival remains poor for metastatic TNBC (mTNBC), we report the case of a patient who experienced a very long response to metronomic chemotherapy, both in first- and second line treatment.

**Keywords:** Triple negative breast cancer; metronomic chemotherapy; oligo metastatic disease

## Introduction

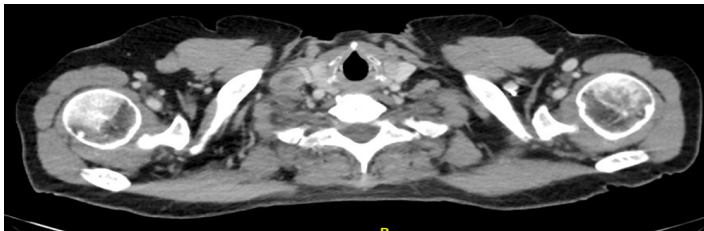
Breast cancer (BC) is the most common malignant neoplasm in women. About 2.3 million of new BC diagnoses and 685.000 BC-related deaths occurred worldwide in 2020 [1]. Triple-negative breast cancer, defined by the absence of estrogenic receptor/progesterone receptor and human epidermal growth factor receptor 2 (HER2) expression, represents approximately 15% of invasive BC. It is mostly associated with premenopausal

status, African-American ethnicity and BRCA 1-2 germline mutation. Characterized by aggressive clinical courses and early recurrence with metastatic spread, it has poor prognosis with a median overall survival (OS) rarely extending beyond 12 to 18 months in advanced disease [2,3]. Metronomic chemotherapy (mCHT) consists of continuous administration of low doses of a chemotherapy agent to maintain prolonged and active plasma concentrations and to provide a favourable safety profile. In addition to a direct antitumor effect, it could explicate its primary action on tumour microenvironment by inhibiting angiogenesis and promoting immune response [4]. Here we present a case-

report of a mTNBC patient who experienced a prolonged response firstly to metronomic oral vinorelbine and then to oral combination of capecitabine (CAPE) and vinorelbine (VNR).

## Case Report

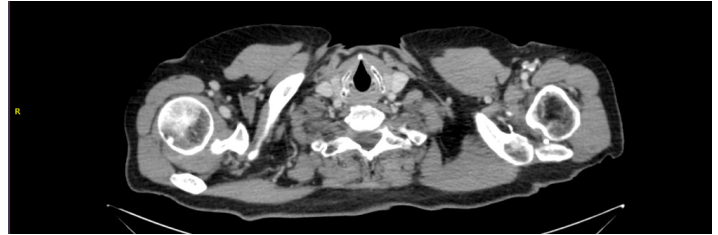
A 72-year-old female patient was referred to our Oncology Unit after a left quadrantectomy plus axillary nodal dissection for a non-special type triple-positive breast cancer (ER/PgR 95/30%, Ki67 25%, HER2 2+ with gene amplification), stage pT1c pN1a (2/8 positive nodes). From October 2010 to May 2012 the patient received adjuvant treatment with epirubicin plus cyclophosphamide for 4 cycles at full dose with only a treatment delay due to a G3 neutropenia which required support with granulocyte growth factors, followed by weekly paclitaxel plus trastuzumab for 12 cycles and trastuzumab every three weeks for 14 cycles. She subsequently underwent radiation treatment on the left breast for a total dose of 50 Gy/5 fractions followed by a boost of 10 Gy/5 fractions on the tumour bed. Based on the tumour biology, in 04/2011 hormone therapy with an aromatase inhibitor was initiated until completion of 5 years. During the follow-up period, in November 2016 a right supraclavicular lymphadenopathy (about 20 millimetres) was detected at the physical examination with the simultaneous rise of the carcinoembryonic antigen (CEA). The staging neck/chest/abdomen computed tomography (CT) and the following positron emission tomography (PET) confirmed the pathological nature of that lesion and excluded other disease localizations. (Figure 1) The subsequent lymph node biopsy showed a different biology, being ER-negative, PR-negative and HER2-negative; so far, it was classified as a TNBC metastasis.



**Figure 1:** Positron Emission Tomography (PET) confirmed the pathological nature of that lesion and excluded other disease localizations.

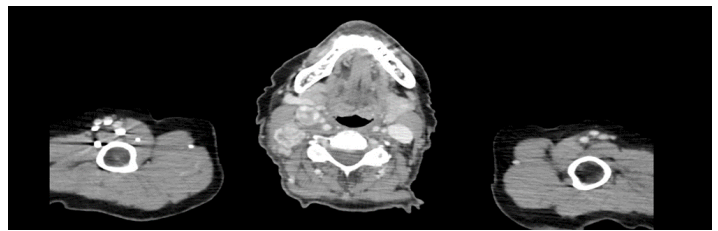
Considering the good performance status (PS ECOG 0), the absence of comorbidities, the presence of a single lesion and the modified tumour biology, after a multidisciplinary discussion, we decided to start radiation treatment on the right supraclavicular fossa (from 27/12/2016 to 09/02/2017 for a total dose of 60 Gy/30 fractions) followed by metronomic single-agent chemotherapy with vinorelbine 40 mg x3/week. The patient obtained a complete response already at the first re-evaluation (Figure 2), because the known lymphadenopathy was no longer appreciable on CT and

on physical examination, with a consensual CEA reduction. The complete response was maintained for 12 months for 17 cycles.



**Figure 2:** The patient obtained a complete response already at the first re-evaluation.

The treatment was globally well tolerated with only a single one-week delay in 03/2022 due to the onset of radiological ground glass alterations at the right lung, treated with levofloxacin. Globally, the patient received 17 cycles, without any grade toxicity. In June 2018, a neck/abdomen/thoracic CT highlighted a disease relapse localized to right lateral cervical lymph nodes (about 12 millimetres), not appreciable on physical examination (Figure 3).



**Figure 3:** CT highlighted a disease relapse localized to right lateral cervical lymph nodes.

Considering the evidence of disease progression and the difference in receptor expression at first relapse, a new node biopsy was performed, unfortunately being non-diagnostic. In October 2018, considering the non-diagnostic result of the biopsy, the low disease burden and the good performance status (PS ECOG 0), a second-line systemic treatment with a further metronomic regimen with Vinorelbine 40 mg for 3 days a week and Capecitabine 1500 mg daily was started. The patient achieved disease stability as best response, which is still maintained in July 2022, date of the last evaluation. The treatment is well tolerated and no delay or dose reduction was necessary until now. Therefore, the treatment is actually ongoing (the patient started the 50° cycle last week) and a new CT is scheduled by the end of October.

## Discussion

Metastatic TNBC is characterized by an aggressive clinical course with a relatively short survival compared with counterpart Luminal tumours. Furthermore, available treatment options, represented by anthracyclines, taxanes, eribulin and platinum

salts, are generally associated with adverse events (Aes) that can lead to treatment discontinuation, mostly in older pts due to the fact that increasing age is a surrogate for increasing comorbidity and loss of function, key factors that relate to treatment choice [5]. Metronomic chemotherapy plays an increasingly important role in this scenario, both by acting on cancer cells with a cytotoxic effect and by modulating the tumour microenvironment (angiogenesis inhibition and immune system stimulation); it also provides a relatively favourable safety profile (both as monotherapy and as combination regimens) representing an opportunity for all those frail patients (such as older ones) for whom other regimens would be difficult to be administered. In this case report, the patient relapsed at a single lymph node station approximately seven months after the end of the hormone therapy. She also received the gold standard therapy with anthracyclines and taxanes combined with Trastuzumab a. interestingly; the tumour biology had changed from the initial diagnosis, turning from a HER2+ to a triple negative disease. As reported by Lindstrom et al, patients with breast cancer can experience altered hormone receptors and HER2 status throughout tumour progression: in particular, ER and PR status changed from positive in primary tumour to negative in relapse in 24.6% and 33.0% of the patients; further, in 14.5%, HER2 status changed between primary tumour and relapse. This phenomenon, which can be possibly explained by the effect of the adjuvant therapies, significantly influences survival: in this study woman with ER-positive primary tumours that changed to ER-negative tumours had a significant 48% increased risk of death compared with women with stable ER-positive tumours [6]. Considering the patient's age and the single site of distant recurrence, it was decided to offer the patient a personalized treatment consisting of radiation therapy on the pathological lymph node followed by a first-line systemic treatment. The first consideration concerns the concept of oligo metastatic disease: Hellman et al first described it in 1995 as a clinical condition characterized by a limited number of metastases ( $\leq 5$ ) and involved organs ( $\leq 2$ ) with controlled primary tumours [7]. Several factors affect the prognosis in breast cancer patients with oligo metastatic disease: the disease-free interval between primary cancer and metastasis formation (DFS), number of metastatic lesions, metastatic sites, and tumour biology and node involvement at diagnosis stage [8]. Once oligo metastatic disease has been defined, the integration of systemic and local treatments to both primary and metastatic lesions may improve outcomes in selected patients with oligo metastatic breast cancer, as demonstrated by both retrospective and prospective studies. In a retrospective study by Weykamp et al evaluating the role of stereotactic body radiotherapy (SBRT) in oligo metastatic ( $\leq 3$  metastases) or oligo progressive (1 progressive lesion) breast cancer patients, after a 21 months follow-up, the 2-year local control (LC) was 89%, distant control (DC) was 44%, progression free survival (PFS) was 17% and overall survival (OS) was

62% [9]. Results from a prospective phase II trial by Trovo et al investigating SBRT or intensity-modulated RT (IMRT) in 54 oligo metastatic breast cancer patients, showed that 2-year LC, OS, and PFS rates with a median follow-up of 30 months were 97%, 95%, and 53%, respectively [10]. Preliminary results from the randomized phase II trial SABR-COMET which enrolled 99 patients (18% with breast cancer) with oligo metastatic disease, randomized to receive systemic therapy plus palliative RT or systemic therapy plus SBRT to all metastatic sites, highlighted a significant improvement in 5-year OS (17.7% vs 42.3%), 4-year PFS (3.2% vs 21.6%), and local control rates (46% vs 63%) in patients treated with SBRT without any significant adverse events [11]. Further prospective randomized studies (SABR-COMET 10, STEREO-SEIN, and NRG-BR002) are currently ongoing with the aim to clarify the role of SBRT to all metastatic sites in oligo metastatic breast cancer.

Regarding the choice of systemic treatment, we decided to start oral vinorelbine 40 mg x3/week (metronomic schedule) obtaining a long disease control with a PFS of approximately 18 months, which appears significantly longer compared to what emerged from the VICTOR-2 and VICTOR-6 trials; furthermore, the treatment was well tolerated, without dose reductions or treatment delays due to toxicity. This strategy was based on the one hand on the SIOG (International Society of Geriatric Oncology) and EUSOMA (European Society of Breast Cancer Specialists) guidelines for the treatment of elderly patients with breast cancer and on the other hand on the results of the VICTOR group studies. The updated recommendations regarding the management of older patients with breast cancer formulated by EUSOMA and SIOG emphasize particular care in avoiding treatment-related toxicities, by including adjustments to treatment schedules and by preferring monotherapy over polychemotherapy regimens when possible; nevertheless, all available chemotherapeutic agents can be used like in younger people [12]. The Victor-2 multicentre phase II trial evaluated the activity and safety profile of the oral metronomic combination of vinorelbine (VNR) and capecitabine (CAPE) in 80 advanced HER2-negative breast cancer patients (pts). In this trial, which represented the first study reporting data on the activity of metronomic VNR and CAPE in TNBC, the subgroup analysis of the TNBC patients (about 35% of the overall population) showed a clinical benefit rate (CBR) of 35.7% with a median duration of CB of 11.3 months; the median time to objective response (OR) and the median progression-free survival (PFS) were 2.1 and 4.7 months respectively, with similar clinical activity when the combination regimen was used in both first- and second-line setting; furthermore it was well tolerated without significant severe adverse events [13]. Results from the recent Victor-6 trial, a multicentre retrospective cohort study which collected data from 584 mBC pts that received mCHT, showed an ORR and disease control rate (DCR) of 17.5% and 64.9% respectively in the TNBC population (97 pts). Best



ORRs and DCRs were observed in first-line settings (20.9% and 76.7%), whereas tumour response decreased proportionally in later lines. Median PFS and OS were 6.01 months and 12.1 months respectively, and they were longer for CAPE-based regimens than for cyclophosphamide (CTX)-based and VNR-based ones. Furthermore, the longest PFS was observed when mCHT was used in first-line setting than for second and subsequent lines. Median OS was 18.2 months for CAPE-based regimens and 11.8 months for VNR- and CTX-based ones, while similar results were observed for OS according to the line of treatment [14]. Montagna et al, in another phase II trial, tested the combination of triple drug oral chemotherapy consisting of vinorelbine, cyclophosphamide and capecitabine (VEX regimen) in 25 previously untreated patients: the overall response rate (ORR) was 27% and the CBR was 50%; median time to progression (TTP) and median time to death were 6.4 and 18.4 months respectively. The VEX regimen was relatively well tolerated with only 9% of grade 3 hand-foot-syndrome (HFS) [15]. At the second disease relapse, once again with an oligo metastatic spread (only later cervical lymph nodes) without visceral localizations, it was decided to continue metronomic chemotherapy adding capecitabine to vinorelbine. The therapeutic choice proved to be successful because the patient obtained a disease stability which persists (the 50°cycle is currently ongoing) without relevant adverse events. This duration of response is extraordinary if we consider that, the median overall survival of mTNBC is around 18 months, as also emerged from the VICTOR-6 analysis of TNBC patients treated with metronomic CAPE-based regimens [14]. This can be partially explained by the change in tumour biology from initial diagnosis to disease recurrence as evidenced by the subgroup analysis of the phase II trial conducted by Montagna et al, in which the PFS rate at 1 year was significantly higher in patients with ER-positive versus ER-negative tumours at primary diagnosis [15]. Furthermore, the low disease burden and the absence of visceral localizations probably represented favourable prognostic factors being expression of a relatively indolent clinical course, a rare behaviour for mTNBC. In addition, the patient tolerated the treatment fairly well; experiencing only grade 1 toxicities that did not require discontinuations, demonstrating that mCHT has a good safety profile. This is consistent with the results of a study conducted by Montagna et al, which didn't highlight cumulative toxicities of metronomic chemotherapy in mBC patients who obtained prolonged clinical benefit for a duration of 12 or more months [16], as well as emerged from the VICTOR-1, VICTOR-2 and VICTOR-6 trials, in which the incidence of grade 3-4 toxicities and the discontinuation rate were very low, demonstrating the favourable safety profile of this type of treatment which makes it suitable for a population of more frail patients such as elderly ones.

## Conclusion

Metronomic chemotherapy represents an effective and generally well-tolerated therapeutic strategy for mBC, including the subpopulation of triple negative pts as demonstrated by the VICTOR group trials. It can bring benefits especially in the setting of frail patients (such as older ones) for whom other chemotherapy regimens would not be indicated. The case we have reported described the clinical course of a mTNBC patient who experienced a very long response to metronomic chemotherapy, both in first- (vinorelbine alone) and in second-line setting (vinorelbine + capecitabine), demonstrating its effectiveness on one hand and its safety profile on the other. In conclusion, further studies are needed to understand the biological mechanisms underlying the maintained response to metronomic chemotherapy over time and to appropriately select the patients who could benefit from it.

**Conflicts of Interest:** The authors declare no conflict of interest.

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