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Treosulfan for advanced breast cancer in a heavily pre-treated patient - a case report

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Summary

Background: Treatment of metastatic breast cancer experienced significant improvement in the past decades by introduction of highly effective therapies, but survival still remains poor. Nonetheless, in some patients, long-term survival can be achieved by sequent endocrine and chemotherapy treatment, although toxicity and resistance eventually occur, until no further suitable and approved therapies remain. If further therapy is needed, therapist may be forced to consider treatments which are promising but not approved, such as the alkylating agent treosulfan, which is approved for the treatment of ovarian cancer only. Thus, relevant clinical data on its use in human breast cancer are lacking. *Case Report:* The authors report the case of a 49-year-old woman with heavily pre-treated, metastatic breast cancer, who experienced complete remission of pulmonary and soft tissue metastases while under treatment with treosulfan. Treatment was generally well-tolerated. *Conclusion:* Treosulfan might be an effective and well-tolerated treatment even in heavily pre-treated patients with metastatic breast cancer.

Key words: Metastatic breast cancer; Salvage therapy; Treosulfan.

Introduction

Breast cancer is the most common cancer in women, with an incidence of 110/100.000 per year [1]. Despite adjuvant therapies, about 30% of patients eventually develop metastatic disease, leading to impaired quality of life and limited survival [1, 2]. While treatment of metastatic disease experienced significant improvement in the past decades by introduction of highly effective drugs as taxanes and anthracyclines, survival remains poor with a five-year survival rate of 21% [2]. Nonetheless, in some patients long-term survival can be achieved by sequent endocrine and chemotherapy treatment. During continuous treatment over months or years, resistance and toxicity will occur, narrowing treatment choices with every subsequent line of therapy, until no further suitable and approved therapies remain. If progress of disease occurs at that point - or the clinical performance of the patient forbids remaining approved but burdensome therapies - therapists may be forced to consider treatments which are promising but not approved.

Treosulfan is an alkylating agent approved for the treatment of ovarian cancer. The drug shows substantial antitumor activity, low toxicity, and has demonstrated substantial activity against human breast cancer cells in animal models [3]. Nevertheless, relevant clinical data on its use in human breast cancer are lacking.

Case Report

The authors report the case of a 49-year-old woman with metastatic breast cancer, who previously received endocrine therapy, anti-osteoclastic therapy, local irradiation and six lines of therapy for metastatic breast cancer, including docetaxel, carboplatin with gemcitabine, 5-fluorouracil with vinorelbine, liposomal doxorubicine, and nab-paclitaxel. Details of previous therapies and clinical history are given in Table 1 and Figure 1.

Table 1. — *Details of clinical history at time of initial diagnosis and before initiation of treosulfan therapy.*

State at initial diagnosis	
Age	42 years
Estrogen receptor expression	Yes (100%)
Progesterone receptor expression	Yes (100%)
Erb2 amplification	No
TNM	pT2 pN2a cM0
UICC Stage	IIIA
ECOG performance status	0
State at start of treosulfan	
Age	49 years
Most recent tumor biopsy	9 months ago
Estrogen receptor expression	Yes (20%)
Progesterone receptor expression	No (0%)
Erb2 amplification	No
Site of biopsy	Liver
Lines of chemotherapy (overall)	6
Lines of chemotherapy for metastatic disease	5
Lines of antiendocrine therapy (overall)	2
Lines of antiendocrine therapy for metastatic disease	1
UICC Stage	IV
ECOG Performance Status	2

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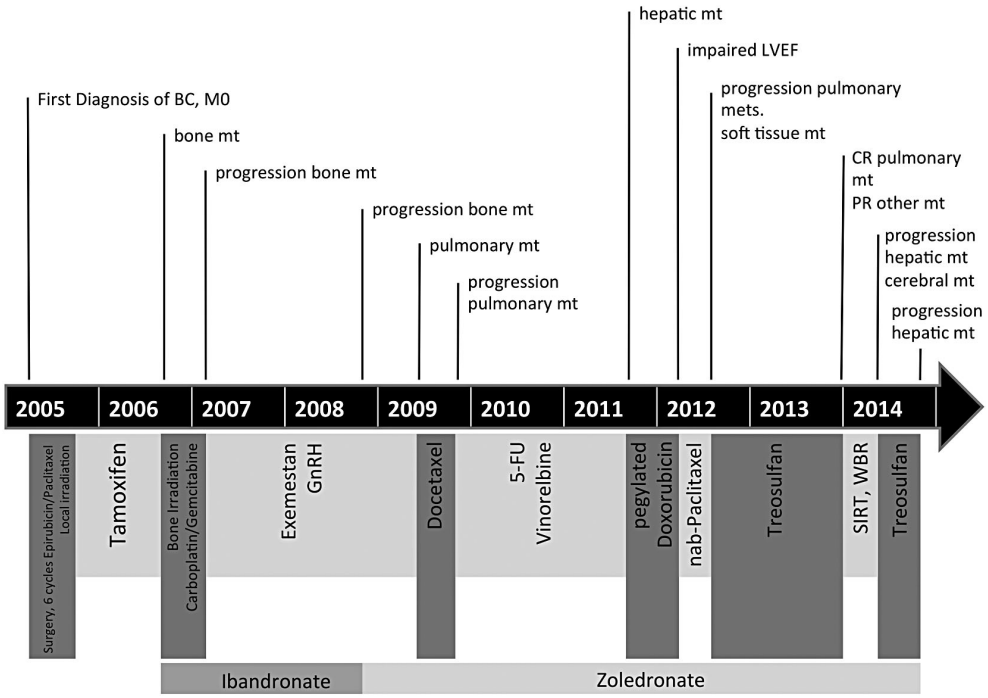

Figure 1. — Timeline of relevant history, procedures, and therapies. BC = breast cancer, mt = metastases, LVEF = left ventricular ejection fraction, GnRH = gonadotropin releasing hormone, 5-FU= 5-Fluorouracil, SIRT = selective internal radiation therapy, WBR = whole brain radiotherapy.

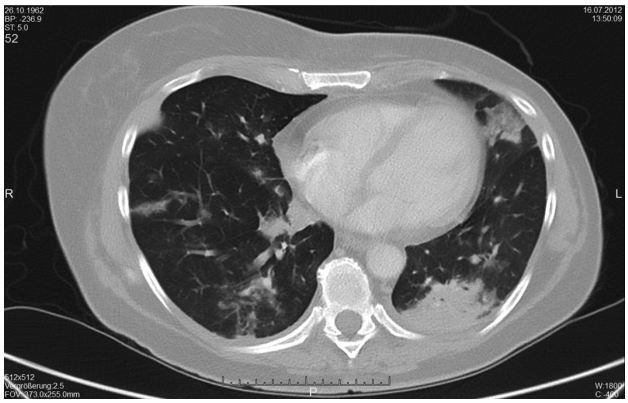

Figure 2. — Thoracic CT-scan, acquired in pulmonary window, previous to initiation of treosulfan in July 2012.

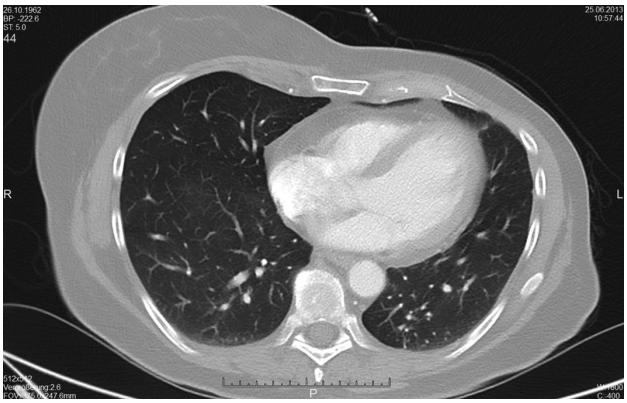

Figure 3. — Thoracic CT-scan, acquired in pulmonary window, after nine cycles of treosulfan in June 2013.

Significant progression of pulmonary, soft tissue, and lymphatic node-metastases occurred under therapy with nab-paclitaxel. The symptoms caused by progression of metastases and the patients demand for further treatment urged the authors to initiate a further line of therapy. Considering the impaired general condition of the patient after six lines of chemotherapy and the palliative approach, they decided to commence a therapy utilizing a well-tolerated agent. Thus, salvage therapy with treosulfan seven g/m^2 body- surface, i.v. every four weeks was initiated.

The patient received nine cycles of treosulfan between August 2012 and June 2013, leading to complete remission of pulmonary and soft tissue metastases (Figures 2 and 3), while hepatic and bone metastasis remained unchanged. At the beginning of the treosulfan therapy, tumor marker CA 15-3 was elevated to 70.9 U/ml (July 2012) and decreased to 11.6 U/ml after nine cycles of treosulfan (June 2013; normal range of local lab: < 25 U/ml). Treatment was generally well-tolerated, with no grade III/IV toxicity occurring at that point. After 12 cycles of treosulfan, patient experienced progression of hepatic metastases, while other metastases remained unchanged. In order to control the isolated progression of hepatic metastases, the patient received selective internal radiation therapy in December 2013, while chemotherapy with treosulfan was paused. In February 2014, the patient was diagnosed with cerebral metastases and received whole brain irradiation. Treatment with treosulfan was recommenced in April 2014, when PET-CT-scan revealed recurrence of pulmonary and soft tissue metastases and progression of bone metastases. The patient then showed prolonged bone marrow depression following every application of treosulfan. Thus, dose of treosulfan was reduced to six g/m² in May 2014 and to five g/m² in July, but the patient was

able to receive only three further applications between April and August 2014. From August to October 2014, the patient received two cycles of treosulfan six g/m^2 every six weeks. Response evaluation in October 2014 revealed substantial progression of hepatic metastases and minor progress of pulmonary and bone metastases. The patient then received two further lines of chemotherapy (carboplatin, followed by eribulin), which had no significant effect on progression of disease. Due to severe toxicity, the patient finally received endocrine therapy in May 2015 and deceased in July 2015.

Discussion

The expectable response to further chemotherapies depends on the extent of previous cytotoxic therapies. Treatment is usually changed if either progression – indicating resistance to the specific treatment – or unacceptable toxicity occurs. Hence, the number of previous antineoplastic therapies might be read as a surrogate for the degree of resistance of the tumor.

As the most efficient agents are usually applied first, it is generally accepted, that the probability of response to a newly initiated therapy decreases with every subsequent line of therapy. When therapy with treosulfan was started in the present patient, she already had received nine lines of antineoplastic therapy, including six lines for metastatic disease, indicating a high grade of resistance of the tumor. Remarkably, therapy with treosulfan achieved partial remission of metastases and even complete remission of pulmonary and soft tissue metastases. As a limitation, it has to be considered that treosulfan therapy was the patients first exposure to the class of alkylating agents, which are known to be highly effective in breast cancer. Arguably, therapy with other alkylating agents as cyclophosphamide might have caused a similar response, but there are neither established regimens for cyclophosphamide (e.g. single agent chemotherapy for metastatic breast cancer), nor is there sufficient knowledge of the toxicity profile as single agent chemotherapy in heavily pre-treated cancer patients. In direct comparison, treosulfan shows better tolerability than cyclophosphamide. Apart from myelosuppression, treosulfan induces none of the typical side effects of the alkylating agents (e.g. ifosfamide, cyclophosphamide, and busulfan) like severe nephro-, bladder, cardio-, and CNS toxicity [4].

A trial investigating efficacy and safety of oral versus i.v. treosulfan in pre-treated, recurrent ovarian cancer recently demonstrated a beneficial safety profile of treosulfan therapy. Remarkably, i.v. therapy resulted in less hematotoxicity than oral application. While quality of life was severely impaired prior to start of treosulfan therapy, quality of life scores ameliorated during therapy, underlining the good tolerability of treosulfan [5]. Thus, treosulfan seems to be a reasonable choice if single agent chemotherapy with alkylating agents is indicated.

After six lines of chemotherapy prior to the initiation of treosulfan administration, the present patient was still naïve to eribulin and thus, formally eligible for a treatment with eribulin.

As demonstrated in the EMBRACE study, treatment with eribulin may lead to prolonged survival in pre-treated metastatic breast cancer patients, while toxicity is reported to be controllable [6]. However, even if some of the participants of the EMBRACE study were heavily pre-treated, only 3% of patients had received six or more lines of previous chemotherapy, including adjuvant treatment. In the present authors' opinion, this impairs significance of the EMBRACE results for this particular case in more than one way: first, it may be assumed that the patients tumor was more resistant to therapy as the average EMBRACE patients. Second, as derived from the authors' clinical experience, the reported toxicity profile of eribulin differs in heavily pre-treated patients. Particularly, if patients experienced previous substantial toxicity as severe neuropathy from taxanes and cardio-toxicity from anthracyclines, the tolerability of eribulin seems to be poorer than described in literature. Thus, the results of EMBRACE are not necessarily applicable to the reported patient. Taking this into account, treosulfan seems to be a favourable choice if general condition of patient is already impaired.

Conclusion

This case demonstrates that treosulfan might be an effective and well-tolerated treatment, even in heavily pre-treated patients with metastatic breast cancer, but further studies are warranted.

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