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Chemoendocrine metronomic therapy of estrogen receptor-positive breast cancer by taxanes or capecitabine in combination with aromatase inhibitors

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Research Article

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Abstract

The intense anticancer therapy using conventional cytostatic drugs is accompanied by serious side effects that restrict the application of the cytostatic drugs. Metronomic therapy as a modern method for administration of low doses of cytostatic agents that in combination with other anticancer drugs induce long lasting tumor dormancy with minimal side effects. **Aim:** We aimed our study at investigation of the efficacy of a contemporary chemoendocrine metronomic therapy, including cytostatic drugs, such as paclitaxel or capecitabine, in combination with aromatase inhibitors (AI, anastrozole, letrozole), in the treatment of estrogen recepor-positive breast cancer. **Presentation of Case:** The patient (74 years old) was initially diagnosed with advanced stage pT4bpN2Mx of infiltrative ductal breast carcinoma with lymph, lung and bone metastases. **Discussion**: Based on high estrogen receptor sensitivity in 67-100% of the analysed tumor cells, endocrine therapy was applied after mastectomy. However, progression of the disease required involvement of systemic cytostatic agents in the therapy. Following the achievements of the contemporary medicine, chemoendocrine metronomic therapeutical protocols, including combination of anastrozole with taxane or capecitabine, were found to induce rapid and continuous disease remission. **Conclusion**: This case report demonstrated rapid achievement of continuous remission by a contemporary chemoendocrine metronomic treatment of metastatic ER-positive breast cancer in all stages of the therapy: systemic anticancer treatment with weekly paclitaxel plus anastrozole, followed by anastrozole plus low doses of capecitabine and analogous maintenance therapy. The results can be explored in future clinical trials about synergy between hormone inhibitors and cytostatic agents in combination anticancer therapies.

Keywords: Anastrozole, Breast cancer, Capecitabine, Chemoendocrine Metronomic therapy, Paclitaxel

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1. Introduction

Cancer is a global disease that causes death of millions of people every year.[1] The incidence of cancer is a complex phenomenon including multifactor genesis of genetically modified malignant cells with abnormal potential for division and metastasis in different tissues. Medication of cancer requires prolonged systemic and maintenance therapy, complementary to surgical treatment. Intense anticancer therapy, involving conventional cytostatic agents (anthracycline antibiotics, cyclophosphamide, fluorouracil, cisplatin, vincristine, etoposide and other DNA-replication or mitotic inhibitors), is accompanied by different side effects (vomiting, nausea, bone marrow suppression, cardio-, nephro-, neuro-, oto-, hemato-, gastrointestinal and other toxicities) that restrict their application especially by patients with accompanying disorders and elderly patients. Taxanes are plant-derived anticancer agents,[2] obtained semisynthetically from species of genus *Taxus* L. (Taxaceae): *Taxus baccata* L. (European yew), formerly from *Taxus brevifolia* Nutt. (Pacific yew). These natural cytostatic agents are highly efficient and less toxic, however they also exhibit some cardiotoxicity and other serious side effects. High standard doses of capecitabine [1250 mg/m^2 twice daily (b.i.d.), days 1–14 every 21 day] can induce erythema and other side effects. In order to reduce the side effects of conventional cytostatic drugs, very low doses of cytostatic agents have been applied in the treatment of breast cancer, gastrointestinal, and other forms of cancer, however most of these studies resulted in short progression-free survival period.[3, 4]

On the other side, metronomic therapy is developed as a modern method for administration of low doses of cytostatic agents that in combination with low doses of other anticancer drugs induce long lasting tumor dormancy with minimal side effects.[5, 6] In this context, chemoendocrine therapy (including combination of tamoxifen with fluorouracil, epirubicin, cyclophosphamide) has been reported to be more effective than endocrine therapy (tamoxifen) alone in terms of improved progression-free survival (PFS, 9 years overall survival rate).[7] Combination of letrozole (aromatase inhibitor, AI) with palbociclib (a cyclin-dependent kinase inhibitor, novel class of drugs) resulted also in significantly prolonged PFS, compared with letrozole alone.[8] High efficacy of chemoendocrine metronomic therapy with low-doses of cyclophosphamide (cytostatic agent) in combination with letrozole (AI) has been demonstrated in clinical trials on primary systemic treatment of estrogen receptor-positive breast cancer patients.[9]

Our study is based on the synergy or additive effect, observed in human breast cancer xenograft models treated with capecitabine (cytostatic prodrug) in combination with tamoxifen or letrozole. Synergy in the concomitant treatment of cancer with two anticancer agents, e.g. hormone inhibitor plus cytostatic agent, is due to the phenomenon that combination of drugs leads to highest anticancer effect than every drug can induce alone in a sequential application. Chemoendocrine treatment of human breast cancer xenografts, reported in the literature, is claimed by the authors to be studied in future clinical trials as independent of the menopausal status of patients.[10]

We aimed our study at investigation of the efficacy of a contemporary chemoendocrine metronomic therapy, including natural or synthetic cytostatic drugs, such as paclitaxel (*Taxus baccata* plant derived agent), or capecitabine (synthetic prodrug of 5-fluorouracil), in combination with AI (anastrozole, letrozole), in the treatment of estrogen recepor-positive breast cancer.[11]

Paclitaxel is a mitotic spindle poison that impedes the microtubule polymer disassembly and induces apoptosis by inhibition of the mitosis.

Capecitabine is a prodrug, metabolised to 5-fluorouracil, which is a thymidylate synthase inhibitor that inhibits the thymidine monophosphate synthesis, necessary for DNA replication.

Anastrozole and letrozole belong to a novel class of drugs, called aromatase inhibitors (AI) that inhibit the enzyme aromatase, (estrogen synthase), thus blocking a key step in the biosynthesis of estrogens.[12] They differ in their mechanism of action from tamoxifen, which is a selective estrogen-receptor modulator (SERM). Tamoxifen exhibits increased risks of uterus cancer, thromboses etc., some of these side effects are reduced by raloxifene, however it has also increased risk of blood clots formation. Aromatase inhibitors have been considered to have superior efficacy and safety for the patients, and therefore AIs were preferred in place of SERM in clinical trials.[13, 14]

2. Presentation of Case:

The patient (74 years old) was initially diagnosed with advanced breast carcinoma and was subjected to palliative right-side mastectomy with partial axillary nodes clear-

ance. The ulcerated tumor measured 3.5 cm in diameter and was staged as pT4bpN2Mx of infiltrative ductal carcinoma. The axillary content consisted of 5 lymph nodes, 4 of which contained metastases. The carcinoma antigen 15-3 (CA 15-3 tumor marker) before surgery was 57 U/ml (ref. 0-31 U/ml), erythrocyte sedimentation rate (ESR) was 77 mm/h (ref. <39 mm/h). Immunohistochemical analyses of prognostic markers revealed week HER2 (human epidermal growth factor 2) expression, positive E-cadherin in all tumor cells, proliferation index Ki-67 14%, estrogen and progesterone receptors expression with high intensity in 67-100% of the cells.

Initial bone metastases were observed before surgery by single-photon emission computed tomography (SPECT-CT) using Technetium radionuclide (^{99m}Tc MIBI).

3. Results and Discussion

Chemoendocrine metronomic therapy using taxane plus aromatase inhibitor (protocol 1).

The disease was diagnosed as pT4bpN2Mx stage of infiltrative ductal breast carcinoma with malignant lymph nodes and initial bone metastases. In the past, in such advanced stage of breast cancer some patients refused to undergo further diagnostic or therapeutic interventions.[15] However, trusting in recent progress of the modern medicine, treatment with aromatase inhibitors, a novel class of drugs, was considered confident of good disease prognosis in our case. Hormonal and chemotherapy were started after mastectomy due to the advanced stage of the disease. Thus, aromatase inhibitor anastrozole (1 mg/day) was included in the initial systemic therapy, based on immunohistochemical analyses, showing high hormone sensitivity of the lesions. In addition, denosumab (XGEVA) was prescribed in combination with calcium and vitamin D for treatment of bone metastases. Denosumab is a novel drug, a remarkable finding of the contemporary science that represents a human monoclonal antibody, binding to the receptor activator of nuclear factor kappa-B ligand (RANKL) in order to inhibit osteoclast development and to prevent fractures caused by bone metastases.

However, 2 months after right-side mastectomy, computed tomography (CT) scan revealed progression of the disease: development of lung metastases and left-side breast tumor formation (1,9 cm in diameter) that were not operated in order to be subjected to chemotherapy.

Due to the disease progression, cytostatic agents were prescribed, but cardiovascular disorder and advanced patient age restricted the range of suitable chemotherapeutics. Consequently, taxanes were selected as medicine of choice. Considering the advanced stage of breast cancer, our attention was drown by novel treatment protocols such as chemoendocrine metronomic therapy, exploring synergy or additive therapeutical effects, effect achieved by concomitant application of cytostatic drugs plus hormone inhibitors. Thus, systemic treatment in this case of metastatic estrogen receptor (ER)-positive breast cancer consisted of weekly paclitaxel (80 mg/m^2), i.v. infusion once every 7 days for 3 weeks, followed by a week rest (a cycle), plus 1 mg anastrozole every day without any interruption (Table 1, protocol 1). Anastrozole was applied as AI because in this case letrozole was found to induce occasional heart flutter.

Weekly paclitaxel was applied in our case only for 3 weeks, because of registered glucose intolerance due to the premedication with antiallergic dexamethasone. In other cases, especially by younger patients, systemic treatment with weekly paclitaxel in combination with anastrozole can be considered for more prolonged application.

Chemoendocrine metronomic therapy using capecitabine plus aromatase inhibitor (protocol 2)

Chemoendocrine metronomic therapy using weekly taxane plus anastrozole (protocol 1) was followed by capecitabine plus anastrozole for 3 months (Table 1, protocol 2): capecitabine (2x1.5 g daily) was given every two weeks, followed by a week rest, plus anastrozole (1 mg daily). AI was given without interruption. After that, a positron-emission tomography/X-ray computed tomography observation (PET/CT) registered no metastases in the lungs, lymph nodes and other organs, the progression of bone metastases was countered. The tumor marker CA 15-3 level was decreased from 57 to 34 U/ml (ref. 0-31 U/ml), ESR was reduced to 40 mm/h (ref. <39 mm/h), HGB was maintained in the range of 116-127 g/L (ref. 120-160 g/L) The RDW index (red blood cell distribution width) was slightly increased (18.7±2.1%, ref. 11.5-14.5%) that is a typical indication of the sensitivity of the patient to capecitabine treatment. The other blood count indices showed disease remission.

Chemoendocrine metronomic maintenance therapy with aromatase inhibitor plus capecitabine (protocols 3 and 4)

After establishment of disease remission, chemoendocrine metronomic therapy was continued in order

Table 1. Chemoendocrine metronomic therapeutical protocols for treatment of ER-positive breast cancer with cytostatic agents in combination with anastrozole as aromatase inhibitor (AI).

Protocol №	Dose of the cytostatic agent	Anastrozole dose q.d.	Duration
1	Paclitaxel 80 mg/m^2 weekly, i.v. infusion once on days 1, 8, 15, followed by a week rest (a cycle)	1 mg	1 month (a cycle)
2	Capecitabine 1500 mg b.i.d., days 1–14 every 21 days (a cycle)	1 mg	3 months (4 cycles)
3	Capecitabine 1,5 g per day, days 1–14 every 21 days (a cycle); this dose can be reduced as in protocol 4.	1 mg	2 years
4	Capecitabine 1000 mg o.d., days 1–14 every 21 days (a cycle)	1 mg	continuously

Abbreviations: o.d. (once a day), b.i.d. (twice daily); t.i.d. (3 times a day); q.d. (every day).

to maintain remission and to prevent disease relapse. Maintenance therapy for 2 years included capecitabine (3x0.5 g daily) for every 2 weeks, followed by a week rest, plus anastrozole (1 mg daily, without interruption) (Table 1, protocol 3). In case of side effects capecitabine dose can be reduced to 1 g daily (Table 1, protocol 4). As a result, tumor marker CA 15-3 level was decreased further from 57 to 25 U/ml (ref. 0-31 U/ml), ESR was at 35±5 mm/h (ref. <39 mm/h), HGB - in the range of 116-118 g/L The RDW index was maintained at 16.4±0.9% (ref. 11.5-14.5%) in conjunction with some increased MCV values (mean red blood corpuscular volume: 98.8±2.6 femtolitres, ref. 82-96 fl) and some decreased RBC values (red blood cells count: 3.7±0.2, ref. 3.7-5.3 T/L). The other blood count indices showed maintenance of the disease remission.

For longer period, this treatment was modified to include decreased dose of capecitabine (1g once daily) for every 2 weeks, followed by a week rest, plus anastrozole (1 mg daily, without interruption) (Table 1, protocol 4).

During all the therapy, the liver and kidney functional indicators (alanine/aspartate transaminases ALT/AST, gamma glutamyl transpeptidase GGT; creatinine, urea) as well as calcium levels were regularly analysed and their values were maintained in normal ranges. Denosumab (XGEVA, 120 mg) subcutaneous injection was administered once every 4 weeks for bone metastases treatment during all stages of the therapy.

On the last but not least consideration, traditional medicine was also applied.[16]

4. Conclusion

Metastatic breast cancer has been considered in the past as incurable disease with an average patient survival rate in the range of 3 years.[17] However, recent achievements of the modern medicine resulted in prolonged survival and improved quality of life of breast cancer patients. This case report demonstrated rapid achievement of continuous remission by a contemporary chemoendocrine metronomic treatment of metastatic ER-positive breast cancer in all stages of the therapy, studied here: systemic treatment with weekly paclitaxel plus anastrozole, followed by anastrozole plus metronomic doses of capecitabine and analogous maintenance therapy.

Rapid and continuous disease remission of the present treatment can be estimated in future clinical trials exploring contemporary therapeutical protocols, such as chemoendocrine metronomic combination of anastrozole (aromatase inhibitor) with decreased doses of taxanes, capecitabine or other cytostatic drugs in primary systemic and analogous maintenance therapy of estrogen receptor-positive breast cancer.

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6. Competing Interests

The authors declare no competing interests.

7. Authors Contributions

Dr. Jian-wei Li and Dr. Xiao-qing Jia contributed to the chemoendocrine metronomic protocols 3 and 4; Dr. D.

Ivanova designed protocols 1 and 2; All authors contributed to writing of the article.

8. References:

1. Stewart BV and Wild CP. World Cancer Report 2014. World Health Organization Press, International Agency for Research on Cancer, Lyon, France; 2014. ISBN 978-92-832-0429-9.
2. Iqbal J, Abbasi BA, Mahmood T, Kanwal S, Ali B, Shah SA, Khalil AT. Plant-derived anticancer agents: a green anticancer approach. Asian Pacific Journal of Tropical Biomedicine. 2017; 7(12): 1129-1150.
3. Bertelsen C, Ji L, Garcia AA, Russell C, Spicer D, Sposto R. Efficacy of very-low-dose capecitabine in metastatic breast cancer. The American Journal of Hematology/Oncology - Breast Cancer. 2015; 11(2): 20-30.
4. Sun JF, Wu RR, Norris C, Noone AM, Amankwa-Sakyi M, Slack R, Marshall JL. Safety of chronic low-dose capecitabine as maintenance therapy in gastrointestinal cancers. Gastrointestinal Cancer Research. 2009; 3(4): 134-140.
5. Montagna E, Cancello G, Dellapasqua S, Munzone E, Colleoni M. Metronomic therapy and breast cancer: a systematic review. Cancer Treatment Reviews. 2014; 40: 942-950.
6. Elzawawy S, Khedr G, Elsabaa B. Maintenance metronomic chemotherapy combined with conventional treatment for metastatic breast cancer patients. Korean Journal of Clinical Oncology. 2015; 11: 80-86.
7. Namer M, Fargeot P, Roché H, Campone M, Kerbrat P, Romestaing P, Monnier A, Luporsi E, Moncuquet P, Bonneterre J. Improved disease-free survival with epirubicin-chemoendocrrine adjuvant therapy compared with tamoxifen alone in one to three node-positive, estrogen-receptor-positive, postmenopausal breast cancer patients: results of French Adjuvant Study Group 02 and 07 trials. Annals of Oncology. 2006; 17: 65-73.
8. Brufsky AM. Long term management of patients with hormone receptor-positive metastatic breast cancer: Concepts for sequential and combination endocrine-based therapies. Cancer Treatment Reviews. 2017; 59: 22-32.
9. Bottini A, Generali D, Brizzi MP, Fox SB, Bersiga A, Bonardi S, Allevi G, Aguggini S, Bodini G, Milani M, Dionisio R, Bernardi C, Montruccoli A, Bruzzi P, Harris AL, Dogliotti L, Berruti A. Randomized phase II trial of letrozole and letrozole plus low-dose metronomic oral cyclophosphamide as primary systemic treatment in elderly breast cancer patients. Journal of Clinical Oncology. 2006; 24(22): 3623-3628.
10. Kataoka M, Yamaguchi Y, Moriya Y, Sawada N, Yasuno H, Kondoh K, Evans DB, Mori K, Hayashi SI. Antitumor activity of chemoendocrine therapy in premenopausal and postmenopausal models with human breast cancer xenografts. Oncology Reports. 2012; 27(2): 303-310.
11. This work was presented on the 4th International Mediterranean Symposium on Medicinal and Aromatic Plants (MESMAP-4), April 18-22, 2018, Antalya, Turkey, abstract book ISBN 978-605-61261-5-4, pg. 125.
12. Gibson L, Lawrence D, Dawson C, Bliss J. Aromatase inhibitors for treatment of advanced breast cancer in postmenopausal women. Cochrane Database of Systematic Reviews. 2009; 4: CD003370. http://dx.doi.org/10.1002/14651858.CD003370.pub3.
13. Eiermann W, Paepke S, Appfelstaedt J, Llombart-Cussac A, Eremin J, Vinholes J, Mauriac L, Ellis M, Lassus M, Chaudri-Ross HA, Dugan M, Borgs M. Letrozole Neo-Adjuvant Breast Cancer Study Group. Preoperative treatment of post menopausal breast cancer patients with letrozole: a randomized double blind multicenter study. Annals of Oncololy. 2001; 12: 1527-1532.
14. Ellis MJ, Coop A, Singh B, Tao Y, LLombart-Cussac A, Jänicke F, Mauriac L, Quebe-Fehling E, Chaudri-Ross HA, Evans DB, Miller WR. Letrozole inhibits tumor proliferation more effectively than tamoxifen independent of HER1/2 expression status. Cancer Research. 2003; 63: 6523-6531.
15. Cserni G. "Revertant" mammary solid papillary carcinoma in lymph node metastasis. Pathology Oncology Research. 2002; 8(1): 74-77.
16. Once a week during therapy 250 g of red beetroot (*Beta vulgaris* L.), known in the folk medicine as antioxidant, strengthening renewal of the red blood cells, was given as a fresh juice together with the juice of 200 g carrots, an orange and an apple.
17. Perez EA. Impact, mechanism, and novel chemotherapy strategies for overcoming, resistance to anthracyclines and taxanes in metastatic breast cancer. Breast Cancer Research and Treatment. 2009; 114: 195-201.