The Breast 21 (2012) 309–313

Contents lists available at SciVerse ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

Increased mean corpuscular volume of red blood cells predicts response to metronomic capecitabine and cyclophosphamide in combination with bevacizumab

Silvia Dellapasqua [a,b,*], Vincenzo Bagnardi [c], Francesco Bertolini [d], Maria Teresa Sandri [e], Davide Pastrello [a,b], Giuseppe Cancello [a,b], Emilia Montagna [a,b], Alessandra Balduzzi [a,b], Patrizia Mancuso [d], Alberto Luini [f], Aron Goldhirsch [b,g], Marco Colleoni [a,b]

[a] Medical Senology Research Unit, Department of Medicine, European Institute of Oncology, Milan, Italy
[b] Division of Medical Oncology, Department of Medicine, European Institute of Oncology, Milan, Italy
[c] Division of Epidemiology and Biostatistics, European Institute of Oncology and Department of Statistics, University of Milan-Bicocca, Milan, Italy
[d] Division of Hematology-Oncology, Department of Medicine, European Institute of Oncology, Milan, Italy
[e] Unit of Laboratory Medicine, European Institute of Oncology, Milan, Italy
[f] Division of Senology, European Institute of Oncology, Milan, Italy
[g] Oncology Institute of Southern Switzerland, Bellinzona & Lugano, Switzerland

ARTICLE INFO

Article history:
Received 27 May 2011
Received in revised form
18 January 2012
Accepted 24 January 2012

Keywords:
Macrocytosis
Metastatic breast cancer
Predictive factor
Angiogenesis
Metronomic chemotherapy
Bevacizumab

ABSTRACT

Background: There is an urgent need for the identification of commonly assessable predictive factors in the treatment of patients with metastatic breast cancer.
Methods: During the course of a treatment including low dose metronomic oral cyclophosphamide and capecitabine plus i.v. bevacizumab (plus erlotinib in one third of the patients) for metastatic breast cancer, we observed that a relevant number of patients developed repeatedly elevated levels of mean corpuscular volume (MCV) of red blood cells without a significant fall in hemoglobin levels. We conducted a retrospective analysis on these 69 patients to evaluate if the increase in MCV could be associated to tumor response.
Results: During the course of treatment 42 out of 69 patients (61%) developed macrocytosis. Using Cox proportional hazards modeling that incorporated macrocytosis (MCV≥100 fl) as a time-dependent covariate, macrocytosis resulted in a halved risk of disease progression (HR 0.45; 95% CI, 0.22–0.92, *p*-value 0.028). In a landmark analysis limited to patients with no sign of progression after 24 weeks of treatment, median time to progression was 72 weeks (48 weeks after landmark) in patients who had developed macrocytosis, and 43 weeks (19 weeks after landmark) in patients who had not ($p = 0.023$).
Conclusion: Macrocytosis inversely related to risk of disease progression in patients treated with metronomic capecitabine plus cyclophosphamide and bevacizumab for metastatic breast cancer. This finding may be explained through thymidylate synthase inhibition by capecitabine. Whether bevacizumab has a role in determining macrocytosis, similarly to what happens with sunitinib, has to be further investigated. If other studies will confirm our findings, macrocytosis might be used as an early marker of response during metronomic treatment with capecitabine and cyclophosphamide with or without bevacizumab.

Introduction

Metastatic breast cancer is considered a chronic disease, where the aim of treatment is the improvement of quality of life and prolongation of survival. Developments in therapeutic interventions for metastatic breast cancer have led to improvements in time to disease progression, time to treatment failure, quality of life, and overall survival.[1–5] Research is now focused on developing novel treatment strategies that might be as effective but less toxic than standard chemotherapy. These new agents may have an important role in the management of patients with metastatic breast cancer due to their favorable safety profiles and lack of cumulative toxicity.

* Corresponding author. Medical Senology Research Unit, Department of Medicine, European Institute of Oncology, Via Ripamonti 435, 20141, Milan, Italy. Tel.: +39 02 57489502; fax: +39 02 57489205.
E-mail address: silvia.dellapasqua@ieo.it (S. Dellapasqua).

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doi:10.1016/j.breast.2012.01.015

Angiogenesis is a key process for tumor development and a relevant target for tumor control.[6] Tumor angiogenesis is regulated by a number of stimulatory and inhibitory molecules, and the vascular endothelial growth factor (VEGF) family of stimulators is the main player in many tumor types, promoting endothelial cell survival, division, migration, as well as vascular permeability and mobilization of immature bone-marrow-derived endothelial progenitor cells into the peripheral circulation.[7] This suggests the need for combined inhibition of multiple pathways or the sequential addition of different antiangiogenic agents, such as bevacizumab, a humanized monoclonal antibody directed against VEGF, as strategies for long term tumor control.[8]

The term 'metronomic' chemotherapy refers to the frequent, even daily, administration of chemotherapeutics at doses significantly below the maximum tolerated dose, with no prolonged drug-free breaks.[9] Many chemotherapeutic agents have been shown to exert cytotoxic effects not only on tumor cells but also on the endothelial cells of tumor microvasculature. This antiangiogenic activity seems prominent with the protracted exposure to low doses of chemotherapeutics, compared with their cyclic administration at the maximum tolerated dose.[10]

The choice of treatment in metastatic breast cancer is usually based on disease characteristics (i.e., estrogen and progesterone receptor status, HER2 overexpression and/or amplification) and patients' characteristics (in particular patients' age, the presence of symptoms, and sites of metastases), and ultimately on patients' preferences. The identification of commonly assessable predictive factors would be extremely useful in the clinical practice, since the single patient could be spared the toxicity of a treatment if this is found to be ineffective to cure her disease.

During the course of a treatment including low dose metronomic oral cyclophosphamide (Endoxan®, Baxter, 50 mg daily) and capecitabine (Xeloda®, Roche, 500 mg 1 tablet thrice daily) plus i.v. bevacizumab (Avastin®, Roche, 10 mg/kg i.v. every 14 days or 15 mg/kg i.v. every 21 days) for metastatic breast cancer, we observed that a relevant number of patients developed repeatedly elevated levels of mean corpuscular volume (MCV) of red blood cells without a significant fall in hemoglobin levels. This finding was previously described by Wenzel et al[11] in 154 advanced cancer patients receiving capecitabine (2500 mg/m2/day for 14 days every 21 days) either as monotherapy or in combination with other antineoplastic agents. A statistically significant increase in MCV (without other hematologic abnormalities or clinical symptoms) could be observed within 9 weeks ($p < 0.0001$). Higher MCV values were seen in patients with tumor remission or stable disease than in patients with tumor progression, but the difference was not statistically significant.

We conducted the present investigation to evaluate if the increase in MCV could be associated to tumor response in metastatic breast cancer patients treated with metronomic chemotherapy in association with antiangiogenic therapy.

Patients and methods

Patients

A total of 69 patients with histologically proven advanced breast cancer were included in the analysis. Patient characteristics at baseline are shown in Table 1.

Forty-six patients received 10 mg/kg bevacizumab (Avastin®, Roche, i.v. every 14 days) in combination with oral cyclophosphamide (Endoxan®, Baxter, 50 mg 1 tablet daily at 9 AM), plus oral capecitabine (Xeloda®, Roche, 500 mg 1 tablet thrice daily after meals) within the context of a phase II trial, as previously described.[12] Twenty-three patients received 15 mg/kg bevacizumab (Avastin®, Roche, i.v. every 21 days) in combination with oral cyclophosphamide (Endoxan®, Baxter, 50 mg 1 tablet daily at 9 AM), oral capecitabine (Xeloda®, Roche, 500 mg 1 tablet three times daily after meals), and oral erlotinib (Tarceva®, Roche, 100 mg 1 tablet once daily either at least 1 h before or 2 h after meals), alone if HER-2 negative ($n = 18$) or in combination with 6 mg/kg trastuzumab (Herceptin®, Roche, i.v. every 21 days, with a loading dose of 8 mg/kg at the first administration) if HER2-positive ($n = 5$) within the context of a second phase II trial (Montagna et al., submitted).

In both trials, response to treatment was assessed every 8 weeks by repeating the same exams used at baseline (either conventional/spiral CT scan or conventional MRI, plus clinical measurements or

Table 1
Patients characteristics at baseline ($N = 69$).

Characteristic	No.	%
Regimen		
BEX	46	67
BEXE	18	26
BEXET	5	7
Age, years		
Median	55	
Range	32–75	
Body weight, kg		
Median	65	
Range	45–99	
Menopausal status		
Premenopausal	24	35
Postmenopausal	45	65
Metastatic sites[a]		
Bone	29	42
Lung	20	29
Liver	24	35
Lymph nodes	25	36
Pleura	8	12
Others	10	14
No. of metastatic sites		
1	34	44
2	24	35
≥3	11	16
Tumor hormone receptor status[b]		
ER positive and PgR positive	15	22
ER positive and PgR negative	29	42
ER negative and PgR negative	25	36
HER2/neu status		
Absent	27	39
1+	29	42
2+	7	10
3+	6	9
Prior neoadjuvant therapy		
No	55	80
CT	9	13
CT/HT	5	7
Prior adjuvant therapy		
No	20	29
CT	12	17
HT	11	16
CT/HT	26	38
Prior therapy for metastatic disease		
No	33	48
CT	3	4
HT	17	25
CT/HT	14	20
CT/HT/trastuzumab	2	3
No. of prior metastatic CT regimens		
0	50	72
1	11	16
≥2	8	12
Prior anthracycline	37	54
Prior taxane	16	23

Abbreviations: BEX = Bevacizumab, Endoxan, Xeloda; BEXE = Bevacizumab, Endoxan, Xeloda, Erlotinib; BEXET = Bevacizumab, Endoxan, Xeloda, Erlotinib, Trastuzumab; ER = estrogen receptor; PgR = progesterone receptor; CT = chemotherapy; HT = hormone therapy.

[a] Multiple sites possible.

[b] Positive: ≥10%.