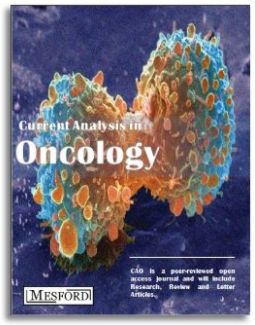
Experience with the Advanced HER2 Positive Breast Cancer Treatment in the Motol University Hospital in the Czech Republic



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Abstract:

In recent years a significant progress is evident in the breast cancer treatment, which leads to the improvement of patients' prognosis and to the prolongation of their overall survival. There are two new drugs, namely pertuzumab (in combination with trastuzumab and chemotherapy) and trastuzumab emtansine (TDM-1) a conjugate antibody and antineoplastic agent –which can be used in aselect group of patients with metastatic HER2 positive breast cancer. Experience gained from our clinical practice has confirmed both the safety of both chemicals and the gained profit for patients.

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Advanced HER2 positive breast tumor, pertuzumab, trastuzumab emtansin, side effects.

INTRODUCTION

In general, it is known that patients with HER2 – positive breast cancer benefit from target therapy byanti-HER2 medications that significantly prolong their median survival.

The aim of this article is to share our experience of clinical practice with the application of these new drugs in patients with locally advanced or metastatic HER2- positive breast cancer. From January 2015 to October 2018, in our workplace 22 patients started a combination therapy with pertuzumab and 24 patients started TDM-1 therapy.

PERTUZUMAB

The key pertuzumab study was Cleopatra which evaluated the effect and safety of pertuzumab + trastuzumab in the 1st line of patients with metastatic HER2-positive breast cancer. The results of the study confirmed a significantly higher response rate in the pertuzumab arm [1].

The combination therapy with pertuzumab is indicated for untreated patients with metastatic or locally advanced breast cancer in a good performance condition. At the same time, the normal ejection fraction condition of the left ventricular (more than 50%according to the echocardiography) must be met. In the Czech Republic, the condition of the combination with docetaxel application may not be complied with thanks to the agreement between the Czech Oncological Society ČLS JEP and the General Health Insurance Company [2]. In case of intolerance of the existing therapies, substitution of docetaxel for paclitaxel is also possible.

The first dose of pertuzumab is set at 840 mg intravenously and is administered for 60 minutes. Each additional application takes 30 minutes and the absolute dose of pertuzumab is 420mg.

The dose of trastuzumab is administered as an initial dosing of 8mg/kg intravenously for 90minutes and each additional dose of trastuzumab is 6mg/kg for 30minutes. These days, a subcutaneous trastuzumab may also be used. Then the absolute dose of subcutaneous trastuzumab is 600mg every three weeks.

Docataxel is given at a dose of 75 mg/m2 for the first cycle and if well tolerated, each additional dose is increased to 100 mg/m2. The dose sequence is pertuzumab, trastuzumab and docetaxel applied last.

If there is a conversion from docetaxel to paclitaxel, then the dose of paclitaxel in a three-week regimen is 175mg/m2, and when it is administered in a weekly regime the dose is 80mg/m2.

In premedication before the actual treatment our workplace uses 500-1000mg of paracetamol per os and a combination of intravenously administered 0.5mg of bisulepin, 16mg of dexamethasone, 1 mg of granisetrone and 20mg of famotidine.

In our file, there are 22 patients who were treated from January 2015 to October 2018. Unfortunately, in 2017 there were no

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Table 1.

Line of Treatment	No Side Effects	GIT G2	Neurotoxicity G1	Neutropenia G3	Neutropenia G4	Neutropenia G4, Anaemiag1	Neutropenia G4, Mucositis G3, Cardiotoxicity
I	8	1	1	2	6	3	1

treated patients, because pertuzumab lost payment in the Czech Republic. At the time of the anti-HER imunochemotherapy initiation, the average age of patients was 53 years (36 – 74 years) and all patients were in excellent condition. All patients had a confirmed HER2 positivity via IHC3+ or ISH and this therapy was their first treatment.

9 patients were without parenchymatous disability and the rest (13 patients) had metastasis in lung, brain or liver. The best response to this therapy was a complete remission in 4 cases, partial remission in 16 cases and only one patient progressed immediately after the first three months of this treatment. On 31st of October 2018, 5 patients continue this treatment. 3 patients discontinued the therapy at their own decision and one of these patients has had complete remission since the end of therapy. It has been34 months on 31st October 2018. One patient had to discontinue the therapy for a generalized allergic reaction to pertuzumab. This patient continued in the combination of docetaxel + trastuzumab and after her intolerance of docetaxel, she is treated by trastuzumab only. In one woman, the HER2-positivity was not confirmed in rebiopsy and one patient had to discontinue her treatment for cardio toxicity. 11 patients discontinued therapy for disease progression. In patients, who discontinued therapy for progression, the average number of pertuzumab + trastuzumab + docetaxel cycles was 12 (2 – 30 cycles). In patients, who discontinued therapy for progression, the average number of pertuzumab + trastuzumab cycles was 19 (2 – 54 cycles). The average duration of the administration of pertuzumab + trastuzumab +/- docetaxel in patients who had already finished therapy was 12.7 months.

This brings us to the toxicity of the mentioned pertuzumab + trastuzumab +/- docetaxel imunochemotherapy combination. The reason, why the docetaxel therapy was discontinued in a limited number of patients, and why the patients were transferred to the combination of trastuzumab + pertzuzumab, is primarily the chemotherapy toxicity.

All patients have alopecia; nobody has nausea, vomiting or diarrhea. 10 patients have musculoskeletal difficulties, fatigue, anaemia, onycholysis and anasarca. All these symptoms disappeared after the discontinuation of docetaxel, which leads to a significant improvement in patients' life quality. Other side effects are listed in Table **1**.

The neutropenia was solved by the administration of growth factors, and the anaemia did not require any intervention.

There were only two serious events .These were cardio toxicity and an allergic reaction. The allergic reaction occurred in a patient during the fifth cycle of docetaxel + pertuzumab + trastuzumab, it developed after the administration of premedication (listed in the introduction of the article) and after the administration of 100ml pertuzumab. The reaction was accompanied by redness in the face, swelling of the mucous membrane of the nose and then followed by hypotension and tachycardia. The patient was conscious throughout entire duration of this reaction. The condition gradually adjusted after the application was discontinued and 300 mg of Hydrocortisone were applied. Further on, the patient continued only with the docetaxel + trastuzumab combination and there were no further difficulties.

In summary, the combination of pertuzumab + trastuzumab + docetaxel is safe and has a very good effect. Patients perceived as subjectively worst the alopecia and onycholysis. However after the discontinuation of chemotherapy, as a result of the pertuzumab + trastuzumab combination the patients' life quality has improved.

TRASTUZUMAB EMTANSIN

The use of trastuzumab emtansin in practice, was authorized based on the Emilia study, a randomized phase III study T-DM1 versus lapatinib plus capecitabin [3]. It demonstrated the superiority of TDM-1 over lapatinib plus capetitabin.

In the Czech Republic, this therapy is intended for patients with HER2-positive metastatic or locally advanced inoperable breast cancer that have been pre-treated with taxanes and trastuzumab. At the same time the following conditions must be fulfilled: either the patients must have been previously treated for locally advanced or metastatic disease; or have cancer that relapsed during the adjuvant application or within six months following the end of the treatment. In the Czech Republic, insurance newly does not cover TDM-1 when a patient was pre-treated with pertuzumab.

In standard dosing TDM-1 3.6mg/kg are administered intravenously and the cycle is tree-weeks. The first application is administered for 90 minutes. When the first cycle is well tolerated, any additional cycle may be shortened to 30 minutes. If toxicity occurs during this therapy, the dosage should be adjusted as recommended: first dose should be reduced to 3mg/kg; second reduction should be to 2.4mg/kg. The treatment should be discontinued if the toxicity continues despite these reductions.

From January 2015 to October 2018 at our workplace TDM-1 therapy began with 24 patients. At the beginning of the therapy, the average age was 58 years (36 – 74 years) and all patients were in excellent performance status (ECOG 0-1). All patients had visceral disabilities and everybody had confirmed HER -2 positivity. All patients were pre-treated with trastuzumab.

In 13 patients, the criterion of using this drug in the second line was met. In other cases, this preparation was used in a

Table 2:

Line of treatment	No side effects	Anaemia G1	Anaemia G1, thrombocytopenia G2, AST G2	AST G1	Neutropenia G1	Neutropenia G3	Neutropenia G4	Trombocytope-nia G2, AST G1	Trombocytope-nia G3
II	6	2		1	1	1	2		
III	2								1
IV	1			1				1	
V	2		1					1	
I	1								

higher line. The best response to this therapy was a complete remission in 1case, partial remission in 8 cases and stabilized disease was confirmed in 5 patients. 10 patients progressed immediately after the first three months of this treatment. Finally, 20 patients discontinued this therapy due to confirmed progressive disease. Three patients discontinued TDM-1 for another reason (their own decisions, thrombocytopenia). One patient continues in this therapy. Of the total 24 patients, 13 patients have died by October 2018. All died of disease progression. The average duration of the administration in patients who had stopped therapy was 8.5 months; the average number of cycles was 11.5 cycles (2 - 54 cycles). The most frequent side effects were neutropenia, anaemia and thrombocytopenia. Only in one case, the treatment had to be discontinued for prolonging thrombocytopenia. Very interesting was the fact that nobody had cardio toxicity. The list of side effects with their relationships to a line order is shown in a Table **2**.

The time of application could be reduced for 30 minutes for all patients due to good tolerance of this treatment.

Generally, TDM-1 is well tolerated and patients describe the subjective improvement of life quality. At the same time, TDM-1 is a safe drug, judging by only one case of a serious event (thrombocytopenia), which led to the discontinuation of the therapy.

CONCLUSION

According to our experience, the referred targeted therapy in patients with advanced HER-2 positive breast cancer improves the prognosis of patients while preserving an excellent life quality. At the same time a minimum of side effects presented themselves and none of them was lethal. The therapy is safe regardless the patient's age and initiation line of therapy. However, we have experienced a more frequent occurrence of adverse effects in patients with the TDM-1 administration in a higher line.

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