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# ABSTRACT

of the dissertation for the degree
of Doctor of Philosophy

# EFFICACY OF LAPATINIB AS SECOND LINE TARGET THERAPY IN PATIENTS WITH HER 2 POSITIVE METASTATIC BREAST CANCER

Speciality: 3224.01 – "oncology"

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Applicant: **Abasov Asıf Ehtıram**

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The dissertation was performed at the National Center of Oncology the Ministry of Health of the Republic of Azerbaijan.

Scientific supervisor: doctor of medical science, professor, honored scinectist,true member of ANAS **Jamil Aziz Aliyev**

Official opponents: doctor of medical science **Abulfaz Agasoltan Soltanov**

doctor of medical science, prof. **Muhammad Muhammadali Karimov**

doctor of medical science **Firuz Arif Abbasov**

Dissertation council FD 1.02 of Supreme Attestation Commission under the President of the Republic of Azerbaijan operating at National Center of Oncology of the Ministry of Health of the Republic of Azerbaijan

Chairman of the Dissertation council: doctor of medical science, professor, honored scinectist, true member of ANAS **Jamil Aziz Aliyev**

Scientific secretary of the Dissertation council: doctor of philosophy in science, **Rashad Saleh Zeynalov**

Azərbaycan Respublikası
Milli Onkologiya Mərkəzi
ELMİ KATİB

Chairman of the scientific seminar: doctor of medical sciences, Professor **Fuad Alovsat Mardanli**

# INTRODUCTION

**The actuality of the subject.**

As well as being the most common type of cancer, breast cancer is also one of the leading causes of death among women. The metastatic form of the disease is more aggressive, especially in delayed cases.[1] Due to their biological characteristics, breast cancer with Her-2 (+) receptor status has a worse prognosis because of its shorter life span and disease-free survival.[2] However, in recent years, a complete study of the biological properties of this receptor has led to its adoption as a target. Drugs such as Trastuzumab, Pertuzumab, T-DM1, Lapatinib, Neratinib, Pyrotinib are drugs that block these targets at various levels and are prescribed in various combinations.[3]

The pereparates for Her-2 target are divided into two main groups: monoclonal anticycles directed against Her-2 and tyrosin kinase inhibitors. Trastuzumab (Herceptin) is the first biological drug against Her-2 and is a monoclonal anticycline that affects the extracellular portion of the receptor.[4-5]

In metastatic tumors, the efficacy of adding Trastuzumab to treatment increased from 32% to 50% compared to patients receiving

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chemotherapy alone, with no disease-free survival ranging from 4.6 months to 7.4 months, and overall life expectancy from 20 to 25 months.[6]

Studies show that Trastuzumaba is more effective in patients with this type of intravenous use of a new target drug Lapatinib. A study investigating the effects of Lapatinib on monotherapy in patients with cerebral metastasis, primarily Trastuzumab, has shown that metastasis is reduced after Lapatinib administration. The results of adding capecitab to treatment improved results by 20%.[7, 8, 9]

Although the results of numerous studies in the literature suggest that Lapatinib has shown positive effects in the treatment of Her-2 (+) breast cancer patients, it is not yet fully understood and awaits solution. For example, the regimen of Trastuzumab + Thaksan, Trastuzumab + Anthracycline (FEC) treatment in patients with Her-2 (+) ER (-) PR (-) metastatic breast cancer, whose prognosis is considered to be worse than those with positive hormonal status, or the combination of Lapatinib + Capecitabine to be more effective has not been investigated enough. It is these statements that confirm the relevance of the purpose and give us a basis for conducting this research.

**The purpose of the study:**

Improvement of line II treatment results by selecting the most effective treatment protocol for patients with metastatic breast cancer with Her-2 (+) ER (-) PR (-) receptor status.

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[8] Blackwell, K.L. Randomized study of lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer / K.L.Blackwell, H.J. Burstein, A.M. Storniolo[ et al.] // Journal Clin Oncol., -2010, 28. - p. 1124–1130.

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**Research objectives:**

1. 6-8 courses in Line I Chemotherapy AC (Doxorubicin + Cyclophosphon), FAC (Cyclofosphan + Doxorubicin + 5 Fluoruracil), FEC (Cyclophosphon + Epirubicin + 5 Fluoruracil), Tac (Paklitaxel), AT (Docorlocellin, AT) Cyclophosphon)

To study the feasibility and effectiveness of treatment with Docetaxel+ Trastuzumab after progression in patients with metastatic breast cancer receiving Trastuzumab.

2. To study the efficacy of postoperative FEC + Trastuzumab treatment for patients with metastatic breast cancer receiving chemotherapy + Trastuzumab in line I.

3. Study of the efficacy of post-progression treatment with Cappecitabine + Lapatinib in patients with metastatic breast cancer receiving chemotherapy + Trastuzumab treatment.

4. Investigation of the separate toxic manifestations of the investigated treatment combinations.

5. Comparison of treatment outcomes for all three groups of patients in the study.

**Materials and methods**

The study was conducted on 186 patients with metastatic BC who received second-line treatment in National Center of Oncology of the Ministry of Health of the Republic of Azerbaijan in 2012-2018. It was an estrogen receptor (ER (-)), a progesterone receptor (PR (-)), and Her-2 (+) in every patients according to immunohistochemistry results. These patients were treated in three study groups. Dosetaxel + Trastuzumab was applied to group I (66 patients), Fluorouracil + Epirubicin + Cyclophosphamide + trastuzumab was applied to group II (58 patients), and Capecitabine + Lapatinib was applied to group III.

Also, patients were equally divided into every group according to predicative factors (age, proliferation index, degree of deterioration, localization of metastases) that could affect treatment outcomes.

Two criteria were mainly used in the study groups: Number of patients with ‘objective’ effect and the period before progression in

patients with an "objective" effect. The median duration of remission, the toxicity of treatment, and the quality of life of patients during treatment were also examined. The results reflected in the absolute figures in the study were traditionally calculated using the Student's Ratio.

**Basic provisions for presentation.**

1.The high efficacy of Lapatinib + Capsitabine in the determination of metastatic breast cancer after progression is confirmed. (objective effect - 58.0%, duration before progression - 11.5 months).

2. It is noted that the use of Dosetaxel + Trastuzumab and FEC + Trastuzumab protocols also has an effect on the treatment of patients in this category: the objective effect in the D + T protocol is 30.3%, the progression is 7.8 months, the FEC + T protocol is 31.0%, and the progression is 8.2 months.

3. When comparing the treatment results of the patients with these protocols, the combination of Lapatinib + Capsecabin is shown to be more effective.

4. Comparative analysis of the toxic effects of all three protocols suggests that the combination of Lapatinib + Capsaicin is a smoother and less toxic protocol.

**Scientific novelty of the- study**

The anti-tumor effect of lapatinib, a new target drug, has been studied in patients with metastatic breast cancer.

Re-administration Trastuzumab and Lapatinib and their assimilation by the body, frequency of toxic manifestations have been developed during the study.

During II line therapy, it has been shown that Lapatinib + Capecitabine protocol is superior to Trastumuzab + chemotherapy in terms of treatment outcomes (both objective and non-recurrent)

**Practical significance of the study.**

The results of the study were discussed by leading chemotherapists of the National Oncology Center of the Ministry of Health of the Republic of Azerbaijan and relevant recommendations were given to other oncology services in the country.

Thanks to research, these patients are receiving stationary treatment (more comfortable for patients) and the number of hospital beds has been reduced. The quality of life is also higher as patients often receive more comfortable treatment at home. Due to the treatment with lapatinib, the corresponding patients are less exposed to toxicity, and the treatment is more effective and longer until the next progression.

**Approbation of dissertation.**

The main materials of the dissertation were presented and discussed at the III Congress of Oncologists of Uzbekistan in Tashkent on May 14-15, 2015, in May 2014 at the scientific-practical conference dedicated to the birthday of national leader Heydar Aliyev in Baku, at the meeting of the Society of oncologists in January 2018, at the inter-departmental Conference of MOM (Baku, October 04, 2019, Protocol No. 1), at the meeting of the scientific seminar on the approbation of PhD dissertations under MOM (Baku, January 17, 2020, Protocol No. 1).

**Publicationand application of the obtained results.** The main theoretical and practical provisions of the dissertation are reflected in 12 scientific papers published. Scientific papers on the topic of the work have been published in Azerbaijan (5 articles, 2 thesis, 1 practical advice ) and in foreign journals (3 articles, 1 thesis).

**Applying the results to practice.**

The results of the present work are presented in the practical work of the National Center of Oncology (NCO) of the Ministry of Health of the Republic of Azerbaijan. It will be used in the educational process and lectures of the oncology department of the Azerbaijan State Institute of Improvement of Doctors named after Aliyev.

At the same time, patients with metastatic breast cancer with Her-2 (+) ER (-) PR (-) will be able to use Lapatinib + Capecitabine for a more effective line II treatment.

The dissertation was performed at the National Oncology Center of the Ministry of Health of the Republic of Azerbaijan.

**The volume and structure of the dissertation.**

The dissertation consists of an introduction (15766 signs), a literature review (51291 signs), a material and methodology section (18200 signs), 3 chapters of personal research, conclusions (93953 signs), results (22213 signs), practical recommendations (2041 signs) and a list of literature (35368 signs), displayed on the 131 computer text (241 829 signs). The dissertation is illustrated with 41 table, 4 diagram and 1 image. The list of literature includes 156 sources, of which 146 are in foreign author.

## MATERIALS AND METHODS OF RESEARCH

The current study includes data from 186 patients withestrogen receptor ER (-), progesteron receptor PR (-), Her-2 (+) metastatic breast cancer, who received second line treatment at the National Cancer Center of the Ministry of Health of the Republic of Azerbaijan in 2012-2018.

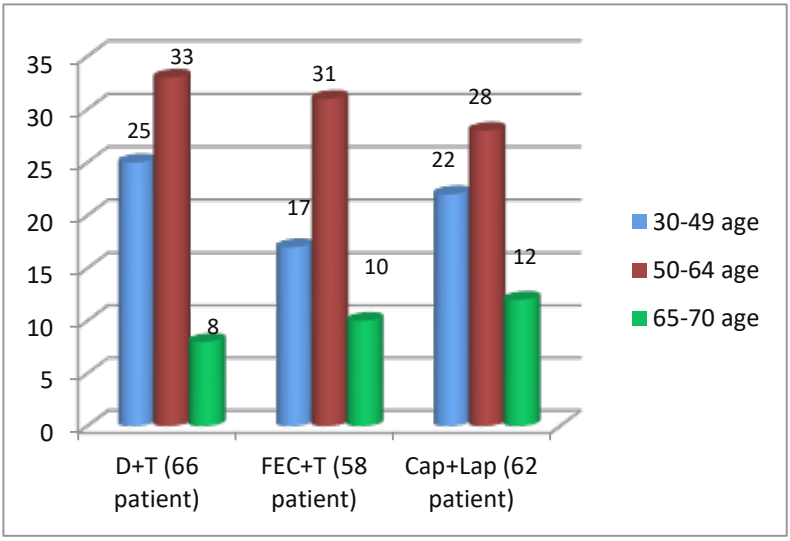
All patients received 6 courses of chemotherapy and "targeted" treatment (with Trastuzumab or Lapatinib) during the II line treatment. These patients were given chemotherapy (6–8 courses with AC, FAC, FEC, AT, TC, or mono Taksan protocols) prior to being included in the study for a year, starting with Target Treatment (Tras-saline 8 mg / kg loading dose, followed by a continuous dose every 21 days. with a 6 mg / kg dose). According to the study, it was also patients who had progression in their disease (lung, bone, brain or joint metastasis in these organs) as soon as 6 months after line I treatment. Of the patients enrolled in the study who completed the recommended course of treatment, only 68 of the I line treatment outcomes were retrospectively studied, while the other 118 patients were prospectively studied.

In all 186 patients, line II treatment was prospectively analyzed and included in the study.

In accordance with the goals and objectives of the study, Her-2 (+) metastatic breast cancer patients undergoing a second line treatment with the intracellular portion of the Her-2 receptor,

subjected to the study of the efficacy and toxic effects of oral tyrosine kinase inhibitor Lapatinib.

Also, patients included in the study were divided into three age groups:




**Graph 1.Division of patients into research and age groups**

The clinical study included patients with diagnosed histologic and immunohistochemical diagnoses.

All patients were age of 70 and subjective status was estimated to be over 50% on the Karnovski scale or ECOG status 1 and 2. In our study, patients with “full effect” and “partial effect” were combined to obtain “objective effect” under the same name.

Two criteria were based on the study groups: the number of patients receiving an "objective" effect and the time until progression in patients with an "objective" effect.

Predictive and prognostic factors that may influence the outcome of treatment are age-specific, localized Ki-67, Grade (degree of histological impairment), and metastasis.

Each patient's heart, liver, and kidney function were within the norm at the time of the study. Also, pathology was not found in general and biochemical indicators of peripheral blood.

At the same time, the main objectives of the study were to determine remission progression medication, toxic effects of treatment, and quality of life of patients during treatment.

All patients were monitored for a specified period of time.

The analysis of the treatment methods used is based on the study of treatment results dated 30.11.2018.

The results, reflected in absolute numbers in the study, were calculated using a traditional statistical parametric method using the Studentcoefficient. This method was used if it was assured that the results were within normal distribution limits. Such verification was carried out with the help of the Westershard rule:if the distribution of the figures is correct, then 99% of all controls should be in the range "m ± 3C" and 50% of the control unit is "m ± 0.7 C" (C is the average quadratic deviation). Then, the mean arithmetic figure (M) and the mean squared deviation - C (calculated from the total number) were calculated. The mean arithmetic error (m) was then calculated.√ M (100- M)/n deviation was used. The formula Tm = M1 - M2 / √ m1 + m2 was used to calculate the difference (n) between the two groups M1 and M2. The difference was correct when it was equal to or greater than T + 2.0.

**Research results and their discussion**

The most important goal of the study was to investigate which Target drug is effective in the treatment of line II treatment of patients with Her-2 (+) metastatic breast cancer.

The feasibility of treatment at that time was determined by the objective effect achieved and the length of the remission period.

All patients received pre-standard 6-course chemotherapy in addition to targeted therapy. 21 days after each course, peripheral blood was analyzed. Repeated courses were conducted when the amount of neutrophilsillarin in peripheral blood was > 20x108/l and platelets > 100,0 x 108 l. If thrombocytopenia or neutropenia was

observed by day 21, treatment was postponed no later than 2 weeks until until the restoration of blood indicators. The protocol of the study did not provide for the reduction of such drugs during the emergence of serious hematological, hepatological and nephrological toxic manifestations. This chapter only describes the results of patients who have completed the planned treatment.

The results of the treatment were evaluated in two stages and evaluated on the RECIST scale.

The results of treatment after 6 courses in each of the three study groups are shown in Table 1 below.

**Table 1**

**General characteristics and treatment outcomes of all patients included in the study**

| Treatment schemes. | The total number of patients | The objective effect | | Stabilization | | Progressiveness. | |
|---|---|---|---|---|---|---|---|
| | | Number of patients | %±m | Number of patients | %±m | Number of patients | %±m |
| D +T | 66 | 20 | 30,3±5,7 | 34 | 51,5±6,2 | 12 | 18,2±4,7 |
| FEC+T | 58 | 18 | 31,0±6,1 | 31 | 53,4,±6,6 | 9 | 15,5±4,8 |
| Cap+ Lap | 62 | 36 | 58,0±6,3 | 22 | 35,5±6,1 | 4 | 6,5±4,9 |
| Total | 186 | 74 | 39,8±3,6 | 87 | 46,8±3,7 | 25 | 12,9±6,2 |

As can be seen from this table, the percentages of objective effects obtained during treatment with the D + T (Group I) and FEC + T (Group II) protocols are almost close to one another30.3 ± 5.7% and 31.0 ± 6.1%, respectively. The results obtained during treatment with the Cap + Lap (Group III) protocol were 58.0 ± 6.3%, which

exceeded both protocols. The Cap + Lap group outperforms the D + T and FEC + T groups, although the study analyzes the patient group as the outcome of treatment 18.2 ± 4.7% versus 6.5 ± 4.9% and 15.5 ± 4.8%, respectively.Patients in all 3 groups were evaluated until treatment progressed until further progression of the disease.

Patients who continued treatment with the Cap + Lap (group III) protocol were 11.5 months ± 5.3, longer than the other two groups, until the next progression. In patients who continued treatment with the D + T (Group I) and FEC + T (Group II) protocols, this period was 7.8 months ± 6.6 and 8.2 months ± 6.1, respectively.

In the study, patients were divided into three age groups (30–49 years – 64 patients; 50–65 years – 92 patients; 65–70 years – 30 patients) and studied separately. The youngest patient was 30 years old and the oldest was 69 years The median age was 54 years. These ages are those that patients have at the time they start treatment in line II.

The objective effect was obtained in 22 of 64 patients in the 30-49 age group, 44 out of 92 patients in the 50-64 age group, and 8 in 30 of the 65-70 age groups.In these age groups, objective effects were obtained in 28% of patients treated with D + T protocols (30-49 years) and 39.4% (50-64 years). None of the patients had any objective effect 8 in the 65-70 age group.An objective effect was obtained in 29.4% (30-49 years), 38.7% (50-64 years) and 10% (60-75 years) patients treated with the FEC + T protocol. To achieve objective effect in 45.5% (30-49 years), 47.8% (50-64 years) and 58.3% (60-75 years) patients treated with Cap + Lap protocolwas made possible.16%, 15.1%, 37.5% of patients with D + T protocol, 17.7%, 9.7% and 30% of patients with FEC + T protocol, 4.5% with Cap + Lap protocol, Progression was noted in 7.1% and 8.4% of patients, and there was a need to change their treatment protocol.

Patients with objective effects in the age groups until the next progression are shown in Table 2.

**Table 2**

**Determining the duration until the next progression in patients with objective effects in different age groups**

| | Number of patients | | | |
|---|---|---|---|---|
| **Age** | **D+T** | **FEC+T** | **Cap+Lap** | **Total** |
| **30-49** | 7,3 month ± 5,8<br>7 patients | 9,0 month ± 2,1<br>5 patients | 12,1 month ± 5,3<br>10 patients | 10,6month ± 5,8<br>22 patients |
| **50-64** | 8,1 month ± 4,8<br>13 patients | 8,0 month± 3,0<br>12 patients | 11,9 month± 3,2<br>19 patients | 9,7 month± 3,6<br>44 patients |
| **65-70** | – | 6,0 month<br>1 patients | 9,8 month± 6,2<br>7 patients | 9,3 month± 5,7<br>8 patients |

Ki-67 is an indicator that plays a universal marker in cell cycle evaluation. Expression of the Ki-67 protein can determine the cell's proliferation activity.In our study, patients with Ki-67 <15% were assessed as low risk group (24 patients), 15-30% as moderate risk group (52 patients), and <30% as high risk group (110 patients).

Of the 24 patients with a Ki-67 index below 15%, a total of 50% had an objective effect and a progression of 12.5%. The objective effect was achieved in 41.7% of patients treated with D + T protocol, 60.0% with FEC + T protocol, and 57.1% with Cap + Lap protocol. At the same time, 25% of patients treated with the D + T protocol had progression and there was a need to change the treatment tactics.

Of the 52 patients with a KI-67 index of 15-30%, 48.1% had an objective effect and 11.5% had progressive progression. An objective effect was obtained in 26.7% of patients with the D + T protocol, in 43.5% -% of patients with FEC + T protocol, and in 78.6% of patients with Cap + Lap protocol, 6.7%. , 17.4% and 7.1% of patients reported progressive progression.

Of the 110 patients with a high proliferation index (30% <), 33.6% had an objective effect and 14.5% had progression. Here, it is

possible to achieve objective effect in 28.2% of patients treated with D + T protocol, 16.7% of patients treated with FEC + T protocol, and 51.2% of patients treated with Cap + Lap protocol. it was possible. However, progression was noted in 20.5% of patients with D + T protocol, 16.6% of patients with FEC + T protocol, and 14.5% of patients treated with Cap + Lap.

Patients with objective effects depending on the Ki-67 index until the next progression are also shown in Table 3.

**Table 3**

**Determining the duration until the next progression in patients whose objective effect is dependent on the Ki-67 index.**

| | **Number of patients** | | | |
|---|---|---|---|---|
| Ki- 67 | **D+T** | **FEC+T** | **Cap+Lap** | **Total** |
| < 15% | 10,5 month ± 7,4<br>5 patients | 13,90 month± 3,0<br>3 patients | 14,9 month± 3.2<br>3 patients | 12.8month± 4,9<br>12 patients |
| 15-30% | 9,8 month± 3,7<br>4 patients | 7,6 month± 6,9<br>10 patients | 12,1 month± 5,0<br>11 patients | 9,9 month± 5,6<br>25 patients |
| >30% | 5,8 month± 3,8<br>11 patients | 6,1 month± 2.1<br>5 patients | 10,6 month± 5,3<br>21 patients | 8,6 month± 4,4<br>37 patients |

**G (grade) -** the degree of histological impairment is an important predictive factor. But it is a subjective parameter. Evaluate the degree of malignancy by assessing three morphological features of a tumor. These are tubular formation, nuclear pleomorphism, and the number of mitoses. Assessments are conducted from 1 to 9:

Grade I (good)3 - 5 points, Grade II (medium) 6 - 7 points, Grade III (bad) 8 - 9 points.

Only 20 of the patients included in the study had Grade I.Seven of them were treated with D + T protocol, 9 with FEC + T protocol and 14 were treated with Cap + Lap. At the same time, objective effect was observed in 28.6% of patients treated with the D + T protocol, in 44.5% of patients treated with the FEC + T protocol, and in 50% of patients

treated with the Cap + Lap protocolobtained. However, progression was noted in 14.3% of patients treated with the D + T protocol, and in 22.2% of patients treated with the FEC + T protocol, and other treatment schemes were changed.Overall, 40% of patients with Grade I had an objective effect and 15% had progression.

The majority of patients, that is, 98 patients had grade II.36.8% of 38 patients treated with D + T protocol, 35.5% of 31 patients treated with FEC + T protocol, 44.9% of 29 patients treated with Cap + Lap protocol the effect was achieved. Progress was also reported in 15.8% of patients treated with D + T protocol, in 6.4% of patients treated with FEC + T protocol, and in 9.2% of patients treated with Cap + Lap.A total of 44.9% of patients with Grade II had an objective effect and 9.2% had progressive progression.

The 68 patients included in the study had a Grade III malice rate.In 19% of the 21 patients treated with the D + T protocol, 16.7% of 18 patients treated with the FEC + T protocol, and 32.4% of 29 patients treated with the Cap + Lap protocol, achieved objective effect. At the same time, progression was noted in 23.8% of patients treated with D + T protocol, 27.8% of patients treated with FEC + T protocol, and 19.1% of patients treated with Cap + Lap protocol. There was a need to change the protocol. A total of 32.4% of patients with Grade III achieved objective effect and progressive progression was noted in 19.1% of patients. Patients who have received an objective effect of Grade (Grade) until the next progression are shown in the table below.

The study included only three organs - lungs, bone and brain, as well as patients with joint metastasis (lung + skull, bone + head brain, and lung + bone + skull). Also, it was the patients who were diagnosed with metastasis when the diagnosis was confirmed and the first line was treated. These patients were not included in the study if metastasis was found in other organs or other treatment methods were used for these patients (radiation of the brain, hygienic amputation of the breast, etc.). Before the second line treatment, a repeated biopsy was performed at the metastasis site.

**Table 4**

**Patients with objective effect of Grade until the next progression**

| | Number of patients with objective effect | | | |
|---|---|---|---|---|
| **Grade** | **D+T** | **FEC+T** | **Cap+Lap** | **Total** |
| **Grade I** | 8,8 month ± 6,8<br>2 patients | 9,6 month± 7,1<br>4 patients | 14,5 month± 6,3<br>2 patients | 10,6month± 6,8<br>8 patients |
| **Grade II** | 8,0 month± 6,7<br>14 patients | 8,3 month± 5,5<br>11 patients | 11,6 ay ± 5,0<br>19 patients | 9,6 ay ± 5,7<br>44 patients |
| **Grade II** | 6,6 month± 5,9<br>4 patients | 6,2 month± 6,8<br>13 patients | 10,9 month± 5,6<br>15 patients | 9,4 month± 5,8<br>22 patients |

In 65 patients, only lung metastasis was encountered. 29 of them were treated with the D + T protocol, 15 were treated with the FEC + T protocol and 21 were treated with the Cap + Lap protocol. Patients had to undergo mandatory computer tomography scanning every three months after the III and VI courses, and only during the targeted treatment. The results of the surveys were compared to the previous ones and formed an opinion on the dynamics of the disease. An objective effect is achieved in 24.1% of patients treated with the D + T protocol, in 20.0% of patients treated with the FEC + T protocol, and in 42.9% of patients treated with the Cap + Lap protocol. However, progression was noted in the D + T protocol by 17.3%, FEC + T by 20.0%, and by 15.4% of patients treated with the Cap + Lap protocol, and it was necessary to change the treatment protocol.Of the 88 patients included in the study, only bone metastasis occurred. Of these, 27 were treated with the D + T protocol, 36 were treated with the FEC + T protocol and 25 were treated with the Cap + Lap protocol. Bone metastases in these patients were still confirmed by osteossintegraphy examination during the first line treatment. Before the second line treatment, patients were subjected to the same screening, followed by an MRI scan in the metastasis zones. At the end of course III and VI courses of chemotherapy, metastasis centers were subjected to MRI scanning every three months only at targeted treatment. Every six months,

patients underwent recurrent osteossintegraphy examination. The results of the surveys were compared to the previous ones and formed an opinion on the dynamics of the disease.

The objective effect of the corresponding protocols was recorded in 44.4%, 41.7% and 72.0%, and progression was 7.4%, 5.5%, and 4.4%, respectively.

In the 33 patients included in the study, brain metastasis was also detected in addition to the lungs and bone organs. In the first line of these patients, 20 had lungs, 12 had bone, and 1 had metastasis in both organs. In the study, 16 patients had lung and skull, 9 patients had bone and brain, and 8 patients had metastases in all three organs - lungs, bones and brain. Treatment was assessed as an objective effect if the size of metastasis in the brain was reduced by more than 25%, and progression was not noted in the lungs and bones.

Here, 10 patients were treated with the D + T protocol, 7 patients were treated with the FEC + T protocol, and 16 patients were treated with the Cap + Lap protocol. The objective effect of D + T was observed in 10.0% of patients and progression in 50.0% of patients. No objective effect was recorded in any patient treated with the FEC + T protocol, with progression of 57.1%.In 56.3% of patients treated with the Cap + Lap protocol, objective effect was reported and only 6.2% had progression. Patients who have received objective effects on metastasis until the next progression are shown in Table 5 below.

**Table 5**

**Patients who receive objective effect of metastasis until the next progression**

| Metastasis | D+T | FEC+T | Cap+Lap | Total |
|---|---|---|---|---|
| Only Lung metastasis | 8,1 month± 6,8 7 patients | 7,6 month± 5,1 3 patients | 10,5 month± 6,3 2 patients | 9,2month± 6,3 19 patients |
| Onlybonemetastasis | 8,9 month± 5,8 12 patients | 11,2 month± 7,1 15 patients | 14,4 month± 6,6 18 patients | 10,6 month± 5,8 45 patients |
| Metastasis of joint (lung, bone, brain) | 6,0 month 1 | 0 | 8,2 month± 6,3 9 patients | 7,9 month± 6,3 22 patients |

Thus, our study found that patients with D + T treatment had a proliferation index of less than 15, with metastasis of Bone Grade II, and was more effective in younger patients. However, during the implementation of the protocol there were some undesirable cases. For example, in 12 (18.2%) patients to whom this protocol was applied, at the initial evaluation (after 3 courses), progression of the disease was noted and other protocols were recommended to patients. At the same time, the use of the D + T scheme has been associated with conventional myelosuppression, as well as gastrointestinal complications, and often with specific toxic manifestations (neuropathy, arthralgia, diarrhea). 354 (89.4%) patients had neuropathy during the course, 265 (66.7%) had arthritis during the course, and 84 (24.1%) had diarrhea during the course. In addition, the technical difficulty of using Dosetaxel (premedication and allergic reactions) has, in some cases, complicated the use of this scheme in patients with specific metastasis and in elderly patients.

When administering the FEC + T protocol, treatment results were slightly superior to the results of the D + T protocol. However, during the implementation of this protocol, there were some undesirable cases. Thus, in 9 patients (15.6%), progression was detected during treatment and the treatment protocol was changed. Also, compared with other protocols, myelosuppression and gastrointestinal complications were more intense and expressed. The main specific complication of this protocol was, of course, cardiotoxicity. Most patients are under the supervision of a cardiologist throughout the course, often receiving parallel cardiac treatments. Previously, this protocol was not applied to patients who were treated with at least 6 courses of anthracycline protocols during the first line treatment.

In general, the FEC + T protocol proliferation index was smaller, with only Grade I and II, with single organ metastasis being noted and more effective in middle-aged patients.

During the application of the Cap + Lap protocol, progression was noted in only 4 patients (6.5%) during treatment.

Among the toxic complications were the most common skin manifestations that could be easily corrected.

Thus, our study has undoubtedly shown the superiority of the new capecitabine + Lapatinib protocol in comparison with conventional Trastuzumab + Chemotherapy protocols. Thus, while the study patients achieved an objective effect of 31.0% in the FEC + T protocol and 30.3% in the D + T protocol, the figure was 58.0% in the Cap + Lap protocol.At follow-up, these patients were estimated to be 8.2 months in the FEC + T protocol for Trastuzumab and 7.8 months in the D + T protocol, but only 11.5 months in the Lapatinib intake protocol.

This factor was more pronounced and more pronounced in those who were treated with the other two protocols than in patients treated with Cap + Lap protocol when looking at toxic complications. Myelosuppression is -10.3% and 11.6% versus 0.8%, and gastrointestinal manifestations are 1.1% - 10.7% and 2.3%, cardiotoxicity wasn`t mentioned butrecorded in other protocols - 5.2% and 0.8%, respectively. Although only toxic skin manifestations were more common in the Cap + Lap protocol than in other protocols, this complication was quickly and easily eliminated.

We also saw the obvious advantage of the Cap + Lap protocol when examining the quality of life of patients receiving treatment. Thus, one of the main concerns for patients receiving FEC + T and D + T protocols was the fact that they had to go to the hospital every 21 days as they were receiving treatment. Given that some patients come from the remote areas to the center and one more patient is nearby, it is considered unacceptable. At the same time, when they were treated in hospital, contacting other severe patients, and sometimes witnessing deaths, gave them additional mental stress and depressive symptoms. It was not accidental that 12 (18.2%) patients receiving FEC + T treatment and 8 (13.8%) patients on the D + T protocol were consulted by a psychoneurologist and received regular treatment. In Cap + Lap, this number was 1 (1.6%).

Patients treated with the Cap + Lap protocol received treatment

at home. Not only did they feel more comfortable with their loved ones but also they did not felt isolated from society and business. They come to the examinations on time, react well to the doctor's orders and receives the treatment with high spirits.

Because of the toxic manifestations, fewer and more mild cases were reported by 16 patients who were on some lighter work. However, among patients with other chemotherapy protocols, this number was about 0.

From all of the above, one can conclude that the objective effect in the treatment of Cap + Lap treatment was greater in the patient, regardless of any prognostic or predictive factors (age, degree of injury, localization of Ki-67, metastasis), and progression in this grouphas been longer. In particular, patients with older and joint metastasis, whose prognosis was considered worse than previously predicted, had more effective outcomes and improved quality of life.

At the same time, no pre- or post-surgical treatment was required during the determination of the Cap + Lap protocol and no antiemetic treatment was prescribed during the treatment. Toxic complications are uncommon, and they are mild and mild. During both chemotherapy and monotherapy with Lapatinib, patients did not come to the hospital except for examinations and were not treated in outpatient or inpatient settings. Patients feel more relaxed and at a higher mood because of they receive treatment at home.

The results further show that Lapatinib treatment results in a higher quality of life than that of treatment outcomes Taking all of this into account, patients in the above-mentioned category are required to select Lapatinib during the treatment of line II.

## RESULTS

1. Lapatinib is highly effective in the treatment of Her2 (+), HR (-), line II treatment of metastatic breast cancer, either in combination with capecitabine or in monotherapy. (Objective effect -

58.0%; duration until progression - 11.5 months) [2, p.59-65], [9, p.42-44 ].

2. The application of the D + T protocol also has an effective impact on the treatment of this category of patients. However, the efficacy was lower than the treatment with the other two protocols (objective effect was 30.3%; duration until progression was 7.8 months) [7, p.81-82].

3. Although the Fec + Trastuzumab protocol was shown to be higher than that of the Docetaxel + Trastuzumab protocol, Lapatinib + Capecitabine was reported in higher numbers.(objective effect - 31.0%, time until progression - 8.2 months) [4,p.169-170],[7, p.81-82].

4. Toxic manifestations are less frequent and mild when treated with lapatinib. Patients' quality of life is higher than those treated with other protocols [2, s.59-65], [5, s.138-140].

5. The treatment results obtained with the Lapatinib + Capecitabine protocol are superior to the results of the other two protocols, regardless of the predictive and prognostic factors [9, s.42-44], [10, s.118-120].

## PRACTICAL RECOMMENDATIONS

1. The diagnosis of Lapatinib should be considered more appropriate when treating patients with any HER-2 (+) metastatic breast cancer compared with Trastuzumabl.

2. Patients' quality of life is not reduced because, the toxic manifestations of the drug is mild.

3. In treating this type of brain metastasis, patients should refuse Trastuzumab and should use Lapatinib.

4. With the treatment of all patients, especially the elderly, Lapatinibi can improve the quality of life along with the non-disease period.

5. Lapatinib's definition should be considered more appropriate in terms of reducing hospital beds and costs in hospitals, as well as facilitating the work of medical personnel.

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Address: AZ 1112, Baku, H.Zardabi st., 79 B

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