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Pharmacoeconomic Evaluation Of Trastuzumab Emtansine And Pertuzumab Treatments In Metastatic Breast Cancer Patients

Metastatik Meme Kanserli Hastalarda Trastuzumab Emtansın Ve Pertuzumab Tedavilerinin Farmakoekonomik Değerlendirmesi

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ABSTRACT

Purpose: Trastuzumab emtansine (TDM-1) and pertuzumab are the relatively novel monoclonal antibodies that use in the treatment of breast cancers. We aimed to investigate the cost-effectiveness of TDM-1 and pertuzumab treatments in patients with metastatic HER-2+ breast tumor.

Method: Patients were detected retrospectively who diagnosed with HER-2+ metastatic breast tumor and treated with pertuzumab or TDM-1 between 11.2016 - 11.2019 in our hospital. Demographic data, drug doses and periods obtained from the patients' medical records. The evaluated pharmacoeconomic outcomes were quality adjusted life years (QALYs), treatment costs and progression-free survival durations.

Results: Treatment with TDM-1 resulted in a mean progression-free survival of 10.5 months. Mean progression-free survival in pertuzumab administered patients was 19 months. In the study, it was determined an additional 1.91 life-years gained, at a cost of 69.334 United States Dollars ($) per QALYs at pertuzumab treatment. Also, it was determined an additional 1.75 life-years gained and a cost of 19.255 $ per QALYs in TDM-1. In pertuzumab treatment, mean progression-free duration was higher compared to TDM-1 ($p < 0.001$). On the other hand, the cost of this treatment was determined to be approximately 3.5 fold higher than TDM-1.

Conclusion: In the study, both treatments were found to be statistically cost-effective. Larger study populations and multi-center studies are needed to more precisely demonstrate the pharmacoeconomic data in this subject.

Keywords: Trastuzumab emtansine, pertuzumab, breast cancer, cost benefit analysis, cost effectiveness

ÖZET

Amaç: Çalışmada trastuzumab emtansin (TDM-1) ve pertuzumab tedavileri uygulanan HER2+ metastatik meme kanserli hastalarda bir maliyet-etkinlik çalışması yapılması amaçlanmıştır.

Metod: 11.2016 ve 11.2019 tarihleri arasında HER2 pozitif metastatik meme kanseri teşhisi konulan ve hastanemizde TDM-1 ve pertuzumab tedavileri alan hastalar retrospektif olarak belirlenmiştir. Demografik data, ilaç dozları ve kullanım süreleri hasta kayıt dosyalarından elde edilmiştir. Değerlendirilen farmakoekonomik çıktılar, kaliteye ayarlı yaşam yılı (QALYs), progresyonsuz sağ kalım süreleri ve tedavi maliyetleridir.

Bulgular: Araştırmada TDM-1 tedavisinde ortalama progresyonsuz sağ kalım süresi 10.5 ay olarak belirlendi. Pertuzumab tedavisi uygulanan hastalarda ise ortalama progresyonsuz sağ kalım süresinin 19 ay olduğu saptandı. HER-2 pozitif metastatik meme kanserindeki maliyet etkililik analizimizde, pertuzumab tedavisinde QALYs başına 69.334 ABD Doları ($) maliyetle ilave 1.91 yaşam yılı kazanıldığı belirlendi. Ayrıca TDM-1 için QALYs başına 19.255 $ maliyetle 1.75 ilave yaşam yılı kazanıldığı saptandı. Pertuzumab tedavisinde progresyonsuz sağ kalım süresinin TDM-1 tedavisine göre anlamlı derecede yüksek olduğu bulundu ($p < 0.001$). Öte yandan, bu tedavinin maliyetinin TDM-1'den yaklaşık 3,5 kat daha yüksek olduğu belirlendi.

Sonuç: Çalışmada, istatistiksel açıdan her iki tedavinin de maliyet-etkin olduğu bulundu. Bu konudaki farmakoekonomik çıktıları daha kesin olarak ortaya koyabilmek için geniş çalışma popülasyonlarına ve çok merkezli çalışmalara ihtiyaç bulunmaktadır.

Anahtar kelimeler: Trastuzumab emtansin, pertuzumab, meme kanseri, maliyet-fayda analizi, maliyet-etkinlik

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Introduction

Breast tumours are the most common cancer type and the foremost cause of cancer-related death among women worldwide. While, approximately 6-10% of new breast cancer cases are diagnosed as metastatic in United States (US), almost 25% of patients have metastases at the initial diagnosis in Far East Asia (De Santis et al. 2017; Bray et al. 2018). According to the latest data in Turkey, 10% of new breast tumor patients are classified as de novo metastatic (Şencan - İnce 2016). The treatment strategy depends on several factors, especially the status of specific biomarkers such as hormone receptors (progesterone and estrogen) and human epidermal growth factor receptor 2 (HER-2). Trastuzumab is a HER-2 receptor blocker monoclonal antibody. It is used in the treatment of both initial stage and metastatic breast cancer patients with HER-2 overexpression (Waks et al. 2019). Trastuzumab administration has been prolonged the mean survival. Therefore, it has been adopted as the standard of treatment in both HER-2 positive metastatic and early stage disease. On the other hand, trastuzumab resistance and relapse after adjuvant trastuzumab is a frequently encountered problem (Mustacchi et al. 2015). Therefore, various novel agents, such as pertuzumab and trastuzumab emtansine (TDM-1) have been developed to strengthen the antineoplastic effects on tumor cells (Kümler et al. 2014).

Pertuzumab is a relatively novel recombinant monoclonal antibody. It inhibits the HER receptor family members like HER-2, HER3, and HER4 which have important roles for cell growth and proliferation (Cortes et al. 2012; Zhang et al. 2014). Pertuzumab is used in treatment at 840 mg loading and 420 mg maintenance standard doses. In the treatment of metastatic breast cancers, trastuzumab (8 mg / kg initial dose followed by 6 mg / kg maintenance dose) and taxane (75 mg/m^2 docetaxel every 21 days or 80 mg/m^2 paclitaxel weekly) are used in combination with pertuzumab for enhancing the anti-tumoural activity in every three weeks (Bianchini et al. 2015; Yu et al. 2016). The other novel agent, TDM-1 is a drug-antibody conjugate that administered as a single agent at 3.6 mg/kg dose in every three weeks to treat metastatic or locally advanced HER-2+ breast tumors (Li et al. 2016; Jain et al. 2018). Pertuzumab and TDM-1 have notably prolonged the survival duration and improved the quality of life of women with HER-2-positive metastatic breast tumor (Verma.et al. 2012; Swain et al. 2013). Pertuzumab and TDM-1 have been approved for use in treatment by the health authority of Turkey in 2016. On the other hand, the usage of these drugs are limited by their cost (Ruiz et al. 2017). These HER-2- targeted therapies cause a tremendous economic burden to the healthcare systems (Diaby et al. 2016). Therefore, it is important to determine the pharmacoeconomic parameters of these novel drugs to make an accurate medical and economic planning. Hence, we aimed in the study to perform a cost-effectiveness analysis for TDM-1 and pertuzumab treatments in metastatic breast cancer patients via determining the mean progression-free survival and treatment costs.

Materials and Methods

This retrospective study was performed according to the principles of the Declaration of Helsinki. Research was approved (10/01/2020-E.655) by the Non-Invasive Clinical Research Ethics Committee of the Pamukkale University. The study was carried out in a public hospital's oncology center in Turkey. Cases consisted of patients older than 18 years of age who had pathologically confirmed HER-2+metastatic breast tumor without a history of any other previous malignancy or chronic disease (hypertension, diabetes mellitus, etc.). Initially, patients diagnosed with HER-2+ metastatic breast tumor and treated with pertuzumab or TDM-1 between 11.2016 - 11.2019 were detected. Demographic data, administered doses, information for calculating quality adjusted life years (QALYs) and the duration of treatment for each patient were retrospectively obtained from the patients' medical records. European Quality 5 Dimension (EQ5D) quality scale was used to calculate QALYs (EuroQol group 1990). Hospitalization charges (laboratory tests, chemotherapy administration fee in an outpatient unit, establishing vascular access, etc.), physician consultation fees, and medical equipment expenses (chemotherapy administration sets and closed system vial adaptors and transfer sets) data were provided by the hospital information management system. The day to day drug expenditures of the patients were obtained by same system in Turkish lira (TL) currency. Then, expenditures exchanged to US Dollar ($) currency by using the daily exchange rates of the Central Bank of Turkey. In the study, the $ was chosen because it is an international currency accepted worldwide. The evaluated pharmacoeconomic outcomes were QALYs, progression-free survival durations and treatment costs. Statistical analysis were performed via using Statistical Package for the Social Sciences, version 22.0 (SPSS 22.0) package program. The Kolmogorov-Smirnov test was used to evaluate the distribution of data. The homogeneity of variance were checked with Levene's test. Percentage, ratio, mean ± standard deviation (X±SD) were used for descriptive statistics. The results of the Kolmogorov-Smirnov test showed that the data did not match the normal distribution. Therefore, the data were compared between groups via Mann Whitney U test. Differences were accepted statistically significant if $p < 0.05$.

Results

Medical records of 91 patients with the diagnosis of HER-2+ metastatic breast tumor were analyzed in the study. However, 11 patients receiving pertuzumab and 7 TDM-1 treated patients were excluded from the study because of the lack of some important data in patient files or they preferred to continue their treatment in other hospitals. Finally, our study groups formed like 31 patients in the pertuzumab and 42 patients in the TDM-1 group. In the study, all the cases consisted of Turkish female patients. Patients in the TDM-1 group were in 38-68 age range and the mean age was 58.4 ± 7.37 while the age range was 21-72 and the average age was 55.7 ± 10.87 in the pertuzumab group. Most of the cases were

married, housewives and primary or high school graduates. The vast majority of patients never used alcohol and smoke cigarettes or quit smoking before the cancer diagnosis. The details of socio-demographic characteristics of patients are summarized in. Table 1.

Table 1. The socio-demographic characteristics of patients

Characteristics	Pertuzumab (n=31)		TDM-1 (n=42)		Total (n=73)	
Marital status	**n**	**%**	**n**	**%**	**n**	**%**
Married	25	80.6	30	71.4	55	75.3
Single	6	19.4	12	28.6	18	24.7
Profession						
House wife	13	42.0	24	57.1	37	50.7
Public servant	8	25.8	9	21.4	17	23.3
Retired	5	16.1	6	14.3	11	15.1
Worker	3	9.7	1	2.4	4	5.5
Farmer	1	3.2	1	2.4	2	2.7
Trader / Self-Employed	1	3.2	1	2.4	2	2.7
Education						
Illiterate	2	6.4	2	4.8	4	5.4
Literate	3	9.7	4	9.5	7	9.7
Primary education	9	29.0	10	23.8	19	26.0
High school	11	35.5	19	45.2	30	41.1
University	6	19.4	7	16.7	13	17.8
Smoking habits						
No/Never	17	54.8	25	59.5	42	57.5
Yes/Quit before cancer diagnose	10	32.2	12	28.6	22	30.1
Yes/Quit after cancer diagnose	2	6.5	3	7.1	5	6.9
Yes/ Continue to smoke	2	6.5	2	4.8	4	5.5
Income level						
Low income	21	67.7	30	71.4	51	69.9
Middle income	9	29.0	12	28.6	21	28.8
High income	1	3.2	-	-	1	1.3
Alcohol use						
No/Never	29	93.5	40	95.2	69	94.5
Yes/rarely	2	6.5	2	4.8	4	5.5
Family history of breast cancer						
No	24	77.4	36	85.7	60	82.2
Yes	7	22.6	6	14.3	13	17.8

TDM-1 is marketed as two different dosage forms as 100 and 160 milligrams vials. Cost differences between 100 and 160 mg vials of TDM-1 were ignored because the difference per milligram was smaller than % 0.2 ($p > 0.05$). On the other hand, pertuzumab is only marketed in the dosage form of 420 milligrams vials. Both of the drugs are the original molecules, have no generics (since 2016 to present) and marketed under the license of the same company (Roche® Müstahzarları San. A.Ş., İstanbul/Turkey) in Turkey. It has been detected various changes occurred in the $/TL exchange rate and the prices of the drugs in the study period. The $/TL exchange rate was 3.1037 in November 2016 while it was 5.7291 in November 2019. The mean $/TL exchange rate was determined as 4.26 ±1.02. It is important to state that there has been price adjustments for seven times in both drugs during the study period. The alterations in mean price per mg of the drugs in the study period is given in Figure 1.

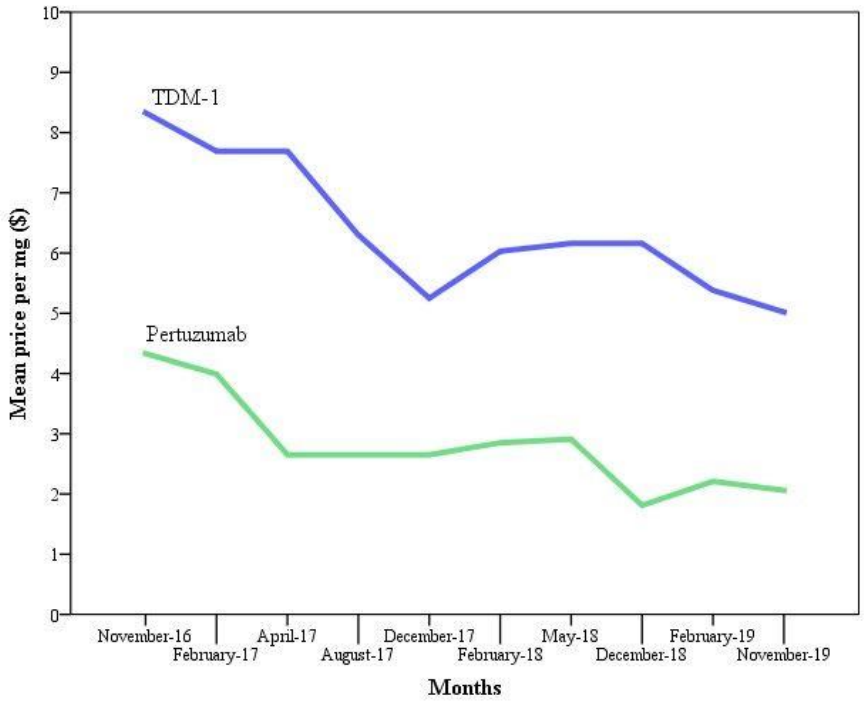

Figure 1. The alterations in mean price per mg of the drugs in the study period

In our study, progression-free survival for TDM-1 was 10.5 ± 2.51 months and the average dose used for a single chemotherapy cycle was 234 ± 14.17 mg. The average drug cost in a single course of chemotherapy for TDM-1 was 1,160 $. Consequently, the total cost of TDM-1 until the progression was calculated as 18,562 $ per patient. Progression-free survival in pertuzumab administered patients was measured as 19 ± 2.27 months. The cost of a single cycle pertuzumab treatment is 1,558 $ and the total cost of pertuzumab from beginning to progression is an average of 40,508 $ per patient. Additionally, it was calculated the mean dose of trastuzumab was 405 mg and the cost was 797 $ for a single cycle treatment while they were 128 mg and 221 $ respectively for paclitaxel. Consequently, the cost of medication per cycle is 2,543 $ concerning the treatment of pertuzumab + trastuzumab + paclitaxel and the total expenditure was calculated as 66,118 $ until progression. In the combination treatment of pertuzumab + trastuzumab + paclitaxel, progression-free survival was found to be notably high compared to TDM-1 treatment ($p < 0.001$). On the other hand, the cost of this treatment was determined to be approximately 3.5 fold higher than TDM-1 treatment. The results of the treatment costs and the other treatment parameters were given in Table 2. Also drug costs and progression free survival periods of the treatments are visually summarized in Figure 2 for better comprehension of the subject.

Table 2. Parameters of the treatment costs*

Parameters	Pertuzumab + trastuzumab + taxane	TDM-1
a- Hospitalization charges per course **	79.50±7.43	79.50±7.43
b- Physician consultation fee per course	11.70±0.49	11.70±0.49
c- Medical equipment expenses per course***	32.50±2.74	32.50±2.74
d- Drug costs per course	2,543.00±110.52	1,160.00±103.58
e- Total treatment costs per course (a+b+c+d)	2,666.7±91.10	1,283.7±86.20
f- Total drug costs until progression	66,118.00±90.95	18,562.00±85.90
g- Total treatment costs until progression	69,334.20±91.00	19,255.50±86.10
h- Progression free survival duration (months)	19.00±2.27	10.50±2.51
QALYs	1.91	1.75

*All data except QALYs were given as (X±SD) and currency in a, b, c, d, e, f, g columns are United States Dollars ($); **Hospitalization charges includes laboratory tests (hemogram and routine biochemistry), chemotherapy administration fee in outpatient unit, establishing vascular access and etc.; ***Medical equipment expenses includes chemotherapy administration sets, closed system vial adaptors and transfer sets used in the cytotoxic drug preparation unit.

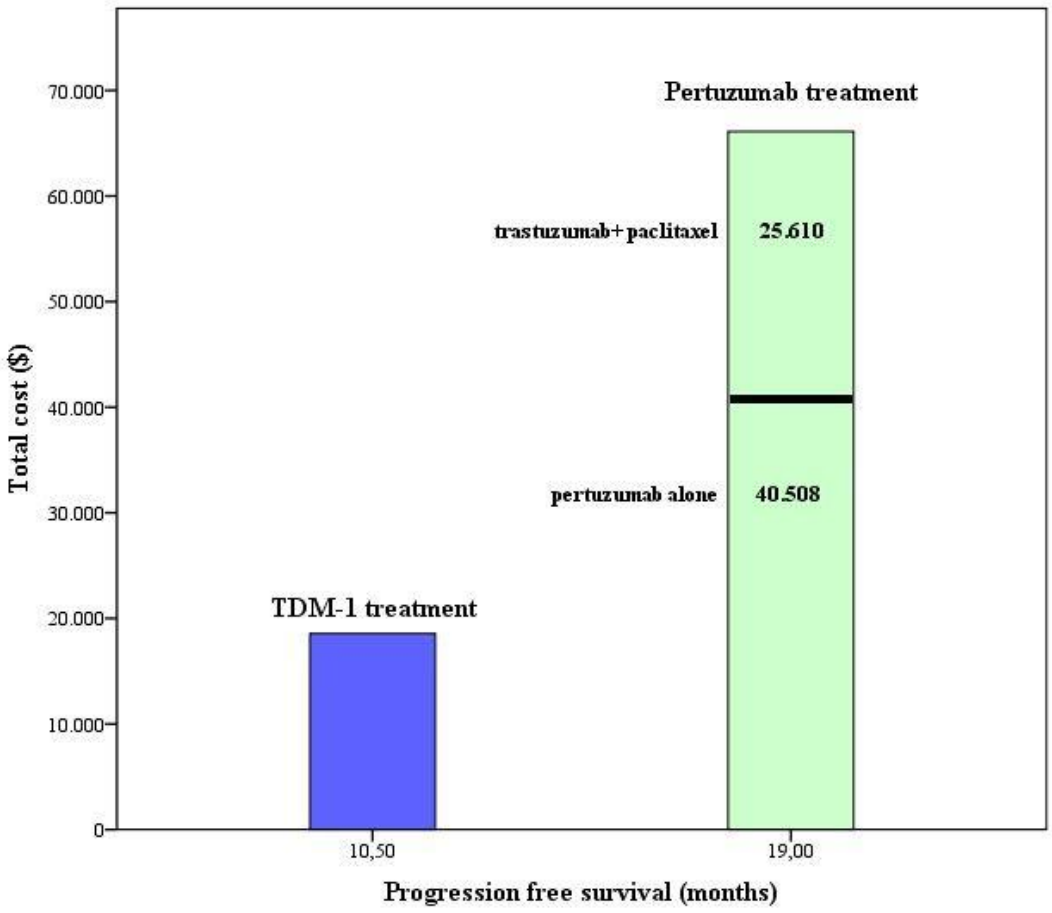

Figure 2. Drug costs and progression free survival periods of the treatments

Discussion

In the study, we evaluated the cost-effectiveness of two different protocols which use in the treatment of metastatic HER-2+ breast cancer. Our findings; QALYs, progression–free survival data and the treatment costs of these novel drugs in Turkish population are an important contribution to literature. On the other hand, the study was carried out in a single-center and with a small number of patients. Therefore, the results of the study cannot be generalized to the entire Turkish population. These were the limitations of our study.

Family history, alcohol and tobacco use are the risk enhancing factors for breast cancer and they are also associated with poor prognosis (Shield et al. 2016; Jones et al. 2017). Interestingly, the majority of the cases in the study consisted of individuals who had no family history of breast cancer and never used alcohol or tobacco products. This situation indicates that other factors (socio-economic status, obesity, birth-control medications, chemical/radiation exposure, etc.) also have an important role both in the formation and poor prognosis of breast cancer. Socio-economic factors such as occupation (working conditions), education level and inadequate income are the foremost social determinants of health. These factors are associated with breast tumor incidence, diagnosis stage, and survival duration (Kohler et al. 2015; Coughlin 2019). In our study, the majority of cases were in the low-income group and graduated from primary or high school. Regardless of ethnicity, breast tumor incidence rates are positively correlated with socio-economic status (Yin et al. 2010). However, low socio-economic status is related with advanced invasive breast tumor risk as well as diagnosis at late stage and poorer survival (Dunn et al. 2010). In this regard our results are consistent with the studies described above.

In the US, the mean life expectancy among women at the age of 51 is 31 years. However, the life expectancy among women who have metastatic cancer recurrence is a bit more over five years (Garrison et al. 2019). Pertuzumab has been confirmed by the US Food and Drug Administration (FDA) for the treatment of patients with HER2+ breast tumor who have not received previous anti-HER2+ monoclonal antibody therapy or chemotherapy for metastatic disease due to demonstrated efficacy in the CLEOPATRA study (Swain et al. 2013). The efficacy of TDM-1 in the treatment of metastatic breast tumor has been shown in the EMILIA trial, in which this treatment compared to the combination of capecitabine and lapatinib (Verma et al. 2012). Both pertuzumab and TDM-1 has been proved to prolong the mean survival in patients with metastatic breast cancer in the studies described above (18.7 and 9.6 months respectively). In our study, it was determined the progression-free survival

of patients administered pertuzumab (19 months) or TDM-1 (10.5 months) were similar with the results of the studies conducted abroad ($p > 0.05$).

The most frequently used methodological types of analysis in the majority of pharmacoeconomic studies are sources for effectiveness, use of incremental cost-effectiveness ratios, and use of QALYs to calculate outcomes to existing results. QALYs is an important parameter commonly used to make an economic evaluation in the field of health. On the other hand, QALYs has several disadvantages, such as assuming that one year of life is the same for everyone regardless of age, gender, etc. and does not take into account other factors affecting the quality of life. Progression in metastatic cancers are related with deteriorated health and quality of life (Beresniak – Dupont 2016; Zhao et al. 2018; Garrison et al. 2019). Therefore, according to the current healthcare practice directives in Turkey, both drugs are reimbursed by the health insurance foundations only until progression of the disease. In our study, progression free survival period data were also used beside the QALYs. In this regard the results obtained in the research are a "real practice data" instead of "estimations." Moreover, guidelines have been generally recommend to perform sensitivity analysis to handle uncertainty. These analyses are performed to determine which variables, when changed, would have a considerable effect on outcomes and expected costs (Zhao et al. 2018; Garrison et al. 2019). On the other hand, in our study period all pertuzumab and TDM-1 treatments were administered to the patients in day-treatment units. Physician consultation fees, hospitalization charges and medical equipment expenses were the same for both treatments as shown in Table 2. Therefore, sensitivity analysis was not conducted in the research because of all other variables were fixed and the only variable was medication prices.

The insertion of pertuzumab to standard trastuzumab + taxane treatment protocol or administering TDM-1 alone as a primary treatment in metastatic HER-2 over expressing breast tumour patients were remarkably raised the overall survival. (Verma et al. 2012; Swain et al. 2013). Both drugs are providing a significant increase in the life expectancy. On the other hand, the usage of these drugs in metastatic cases are limited by their costs. In a pharmacoeconomic analysis conducted with 8360 participants in US was reported treating the advanced stage breast cancer is related with significant rises in expenses when compared with early stage cases. It is highlighted in the study the cost of breast cancer treatment can significantly diminish by early diagnosis (Blumen et al. 2016). In the study, total drug cost of TDM-1 was 18,562 $ while it was 66,118 $ for pertuzumab + trastuzumab + taxane combination. In our cost - effectiveness analysis in HER-2 positive metastatic breast tumor resulted in an extra 1.91 life-years gained, at a cost of 69.334 $ per QALYs gained in pertuzumab treatment. Also, it was determined an extra 1.75 life-years gained and a cost of 19.255 $ per QALYs gained in TDM-1 treatment. Considering the prolonged progression free survival period, gained QALYs, and costs of drugs both treatments were found to be cost-effective in our study.

The number of pharmacoeconomic studies concerning pertuzumab and/or TDM-1 in metastatic breast cancer is so limited. In a cost-effectiveness analysis study of pertuzumab treatment in HER-2 positive metastatic disease, resulted in an extra 1.81 life-years gained, at a cost of 472,668 $ per QALYs gained. It was reported in the study pertuzumab + taxane + trastuzumab administration in metastatic cases is not cost - effective in the US (Durkee et al. 2016). In another cost-effectiveness study of targeted therapies in metastatic HER-2 positive breast cancer in the US reported the combination of pertuzumab, trastuzumab, and taxane (docetaxel) as primary therapy, TDM-1 in second step therapy, and lapatinib/capecitabine as tertiary resulted in 1.81 QALYs, at a cost of 335,231 $. The combination of docetaxel/ trastuzumab as primary without subsequent TDM-1 or pertuzumab provides 1.41 QALYs, at a cost of 175,240 $. It was suggested in the study pertuzumab + trastuzumab + taxane as primary therapy, subsequent TDM-1 as second step therapy, required approximately a 50% discount in the total drug cost for considering as a cost-effective strategy (Diaby et al. 2016).

In a novel study conducted in Taiwan, the cost of pertuzumab + taxane + trastuzumab combination was determined as 593,741 $ per QALYs. The results of the study indicated pertuzumab + taxane + trastuzumab could be named as a rational treatment option if the costs could be reduced 10%. It was reported in the study pertuzumab + taxane + trastuzumab combination can be a pharmacoeconomic option as a primary treatment only under convenient drug costs (Leung et al. 2018). In a similar study conducted in Mexico the estimated incremental cost-effectiveness ratio for pertuzumab + taxane + trastuzumab followed by TDM-1 and then capeticabin/lapatinib in Mexico to be approximately around 270,000 $. It was reported in the study that the pertuzumab or TDM-1 treatment protocols were not cost effective compared with the combination of taxane and trastuzumab as first line without subsequent TDM-1 or pertuzumab in terms of public perspective. (Diaby et al. 2017).

Considering the results of our study and the other researches mentioned above, survival data and QALYs in all these studies are found to be similar to each other. On the other hand, there are significant differences between studies in terms of cost of per QALYs gained. Prices of the drugs may vary among the countries according to their national income level and price adjustment policies. However, even though the cost of original drugs are cheaper in middle and low income countries, their affordability is fewer compared to high income countries (Prasad et al. 2017).

Conclusion

It is important to note that the clinically most effective treatment protocol is not the most cost-effective choice always. Pharmacoeconomic studies are required to determine the more cost-effective therapy options. This is the first pharmacoeconomic research evaluate the TDM-1 and pertuzumab in the treatment of HER-2-positive metastatic breast cancer in Turkey. The results showed that both of

these treatments are cost-effective. However, for a more rational medical and economic planning, other treatments such as lapatinib, eribulin, and nivolumab used in breast cancer should be taken under consideration. Larger study populations and multi-center studies are necessary to demonstrate the cost-effectiveness of pertuzumab and TDM-1 treatments in the Turkish population more precisely.

Conflict of Interest: The authors have no conflicts of interest to declare.

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