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ORIGINAL ARTICLE

Pharmacotherapeutic recommendations for application of target oncological drug therapies for treatment of breast cancer in Bulgaria – therapeutic efficacy and cost effectiveness

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Summary

Purpose: *The purpose of this study was to determine the direct costs of targeted cancer therapies for the treatment of breast cancer, calculating the effectiveness of the additional costs (ICER) and the cost of life years gained (LYG), using data from randomized clinical trials cited in the summary of product characteristics (SPC) of medicinal products approved for use under the centralized procedure.*

Methods: *Data from the SPC and clinical trials was analyzed. ICER and LYG of the medicinal therapies were compared using data from Phase III clinical trials cited in the Summary of product characteristics. The perspective of the payer was adopted.*

Results: *The SPCs of five drugs were analyzed. Targeted therapies were compared to placebo or to best supportive care (BSC) in some of them, while in others monoclonal antibodies (mAbs) and tyrosine kinase inhibitors were compared to existing drug therapies. Cost-effectiveness of each therapy was calculated. The value of ICER was between 56 470 Bulgarian Levs/LYG and 879 480 Bulgarian Levs/LYG.*

Conclusion: *The current pharmacotherapeutic recommendations for targeted therapies for the treatment of breast cancer are based on evidence of therapeutic efficacy and cost effectiveness. Their application in therapeutic practice in Bulgaria is necessary to ensure patient access to effective therapies within the limited public funds.*

Key words: *breast cancer, cost-effectiveness, pharmacoeconomics, QALY, targeted therapies, therapeutic guidelines*

Introduction

The incidence of breast cancer in Bulgaria has been increasing by 1.8% on average every year. However, mortality remains statistically unchanged. Breast cancer is the most frequent disease in women and it represents 26.4% of all malignancies [1]. In 2012, 3923 new cases were registered (incidence 104.6 per 100 000) and 1364 women have died in the same period (36.4 deaths per 100 000). The incidence of breast cancer increases with age after 35 years and reaches its peak in the age group 65-69 years (234.3 per 100 000) [2].

The incidence of breast cancer in Bulgaria is higher than the EU average. Data for 2012 show incidence of 104.6 per 100 000 women when the EU average rate is 94.2 per 100 000 women. Mortality from breast cancer in Bulgaria is also higher than the EU average - 36.4 to 23.1 per 100 000 women respectively [3].

The five-year relative survival rate from the disease in our country is 72.8%, which is also lower than the EU average - 83.8% [3]. Projections for 2015 provide 4107 newly diagnosed cases of breast cancer and 1394 deaths [2].

The available statistical data justifies the significance of the disease and the constantly in-

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creasing public expenditure on its treatment.

According to the medical standards for the treatment of breast cancer, issued by Bulgarian Cancer Society (BCS), the target drug therapies are recommended for adjuvant therapy (trastuzumab) and for the treatment of recurrent or metastatic disease, as follows: bevacizumab in combination with capecitabine patients resistant to treatment with anthracyclines and taxanes; systemic therapy with overexpression of HER2 – pertuzumab+trastuzumab+docetaxel; trastuzumab; trastuzumab+paclitaxel; trastuzumab+docetaxel; trastuzumab+capecitabine; trastuzumab+lapatinib; trastuzumab emtansine; lapatinib+capecitabine [4].

Bulgarian Cancer Society therapeutic recommendations are not consistent with published comparative studies of therapeutic efficacy and cost-effectiveness, nor with the current legislation in Bulgaria - only medicinal products included in the positive list of medicines are reimbursed with public funds (to February 2015 trastuzumab emtansine is not included in the positive drug list (PDL). The regulations provide medicines for cancer to be reimbursed by the National Health Insurance Fund (NHIF), once incorporated in the PDL and the prices and the level of reimbursement are determined by the National Council on prices and reimbursement of medicinal products (NSRLP) [5].

According to NHIF, the cost of cancer therapies in Bulgaria is growing much faster than the gross domestic product (GDP) of the country. In 2012, in the NHIF budget for cancer treatment provided 57 million BGN; in 2013 - 90 million BGN, and in 2014 - 145 million BGN. Annually the deficit exceeds 30% [6]. For 2015, 175 million BGN are provided in the NHIF budget for cancer therapies [7]. The growth of the costs exceeds 70% annually for the period 2012-2015. Due to the increasing number of patients suffering from cancer, the cost of medical care and drug therapies will continue to increase in the coming years.

The lack of comparative pharmacoeconomic evaluations and consensus on the cost-effectiveness threshold for QALY (LYG) for innovative targeted cancer therapies, before deciding on their remuneration with public funds from NHIF is one of the main reasons for the unmanaged growth of costs. This requires the development of pharmacotherapeutic recommendations for application of targeted drug therapies based on evidence of therapeutic efficacy and cost effectiveness.

The purpose of this study was to determine the direct costs of targeted cancer therapies in the treatment of breast cancer, calculating the effectiveness of the ICER and the cost of LYG, using data from randomized clinical trials cited in the summary of SPC of medicinal products approved for use under the centralized procedure under Regulation (EC) No.726/2004 of the European Parliament and the Council of 31 March 2004.

Methods

Five targeted therapies approved for the treatment of breast cancer by the European Medicines Agency, available in Bulgaria and recommended by BCS (bevacizumab, trastuzumab, lapatinib, pertuzumab, trastuzumab emtansine) were included in the study. ICER and LYG of the medicinal therapies were compared using data from Phase III clinical trials cited in the summary of product characteristics. Therapeutic efficacy was defined as an extension of the median overall survival (OS) and survival without disease progression (PFS). Treatment costs were calculated on the basis of the reference prices in the PDL to February 2015. The average duration of treatment and the applied dose regimen were described in the analyzed clinical trial data. The study did not include other direct or indirect

Table 1. Data from trials of targeted cancer drug therapies for the treatment of breast cancer

No.	*Drug*	*First author, year [Ref]*	*Test group - therapy*	*Control group - therapy*
1.	bevacizumab	Gray, 2009 [9]	BEV + PAC (HER2+)	PAC (HER2+)
2.	bevacizumab	Pories et al., 2010 [9]	BEV + CAP (HER2-)	CAP (HER2+)
3.	trastuzumab	Rugo et al., 2010 [10]	TRA (HER2+)	PLA (HER2+)
4.	trastuzumab	Triparthy et al., 2004 [11]	TRA + PAC (HER2+)	PAC (HER2+)
5.	trastuzumab	Marty et al., 2005 [12]	TRA + DOC (HER2+)	DOC (HER2+)
6.	lapatinib	Cameron et al., 2010 [13]	LAP + CAP (HER2+)	CAP (HER2+)
7.	lapatinib	Pivot et al., 2015 [14]	LAP + CAP (HER2+)	TRA + CAP (HER2+)
8.	lapatinib	Blackwell et al., 2010 [15]	LAP + TRA (HER2+)	LAP (HER2+)
9.	lapatinib	Johnston et al., 2009 [16]	LAP + LET (HER2+)	LET (HER2+)
10.	pertuzumab	Swain et al., 2014 [17]	PER + TRA + DOC (HER2+)	TRA + DOC (HER2+)

BEV: bevacizumab, PAC: paclitaxel, CAP: capecitabine, PLA: placebo, TRA: trastuzumab, DOC : docetaxel, LAP: lapatinib, PER: pertuzumab, LET: letrozole

Table 2. Therapeutic efficacy of the analyzed target cancer therapies for the treatment of breast cancer

No.	Drug	OS – median, months		PFS – median, months	
		Control group	Test group	Control group	Test group
1.	bevacizumab	24.8	26.5	5.8	11.3
2.	bevacizumab	–	–	6.2	9.8
3.	trastuzumab	–	16.4	–	3.2
4.	trastuzumab	17.9	24.8	3.0	7.1
5.	trastuzumab	22.7	31.2	6.1	11.7
6.	lapatinib	16.5	18.5	4.6	6.0
7.	lapatinib	27.3	22.7	8.0	6.6
8.	lapatinib	9.5	14.0	2.0	3.0
9.	lapatinib	90.6	93.4	3.3	8.9
10.	pertuzumab	37.6	–	12.4	18.5

OS: overall survival, PFS: progression free survival

health costs, because it was assumed that their differences were negligible for the result. A health perspective and the perspective of the payer, the NHIF, were adopted.

ICER is calculated as the additional cost of a new drug therapy for an improved clinical outcome, as indicated below:

$$ICER = \frac{Costs\,(A) - Costs\,(B)}{Efficiency\,(A) - Efficiency\,(B)},$$

where:
A: new therapy
B: current therapeutic alternative in Bulgaria

In cases where the new drug therapy had better efficiency and lower cost, then it was considered dominant and the ICER was not calculated.

Results

The SPCs of five drugs were analyzed. Targeted therapies were compared to placebo or to BSC in some of them, while in others mAbs and tyrosine kinase inhibitors were compared to existing drug therapies. Trastuzumab emtansine was not included in this study because to February 2015 is not included in the PDL in Bulgaria. Data from clinical trials of the other four medicines are presented in Table 1.

The results of the comparative studies on the established therapeutic efficacy provided by OS and PFS, obtained in the tests compared to the control group are presented in Table 2.

Gray et al. [8] and Pories et al. [9] concluded that adding BEV to CAP or PAC therapy in the treatment of HER2- breast cancer achieves a lengthening of PFS between 3.6 and 5.5 months, but in practice it had minimal impact on the final health results like the OS rate. Clinical studies of drug therapies including trastuzumab, in the treatment of patients with overexpression of HER2 (HER2 +). Tripathy et al. [11], Rugo et al. [10], and Marty et al. [12] demonstrated that monotherapy and combination therapy with docetaxel or paclitaxel offered significant benefits in the patient in terms of both PFS (extending between 4.1 and 5.6 months), and in terms of OS (extending between 6.9 and 8.5 months). In the performed analysis of the efficacy, the results from four clinical trials are included.

Cameron et al. [13] concluded that the addition of lapatinib to therapy with capecitabine prolonged the average PFS and OS by two months.

Pivot et al. [14] compared the efficacy of lapatinib + capecitabine to trastuzumab+capecitabine and found that lapatinib+capecitabine was inefficient therapy concerning PFS (-1.4 months) and OS (-4.6 months).

Blackwell et al. [15] found that the combination of trastuzumab+lapatinib achieved better results compared to monotherapy with lapatinib, concerning PFS (+1.0 month) and OS (+4.5 months).

The addition of lapatinib to the treatment with aromatase inhibitors (letrozole) contributed to the increase of PFS to 5.6 months and of OS to 2.8 months [16]. Swain et al. [17] investigated the addition of pertuzumab to the combination of trastuzumab+docetaxel and proved that it prolongs PFS by 6.1 months, while the OS has not been reached.

The cost of adding mAbs and tyrosine kinase inhibitors in existing therapies for metastatic or recurrent breast cancer was calculated for each treatment cycle until disease progression in reference prices in Bulgaria PDL to February 2015 and are presented in Table 3.

Table 3. Added costs for targeted therapies for the treatment of breast cancer for a period up to progression (Bulgaria, February 2015)

No.	*Drug*	*Dosage and method of administration*	*PFS, months*	*QMPTC, mg*	*RPAP, BGN/mg*	*AEP, BGN*
1.	bevacizumab	10 mg/kg every two weeks	11,3	17 500	7,1196	124 593
2.	bevacizumab	15 mg/kg every three weeks	9,8	14 700	7,1196	104 658
3.	trastuzumab	8 mg/kg FTW, 6 mg/kg NTW	3,2	2240	9,45353	21 176
4.	trastuzumab	8 mg/kg FTW, 6 mg/kg NTW	7,1	4760	9,45353	44 999
5.	trastuzumab	8 mg/kg FTW, 6 mg/kg NTW	11,7	7280	9,45353	68 822
6.	lapatinib	1250 mg/daily	6,0	225 000	0,14738	33 160
7.	lapatinib	1250 mg/daily	6,6	247 500	0,14738	36 477
8.	lapatinib	1000 mg/daily	3,0	2240	9,45353	21 176*
9.	lapatinib	1500 mg/daily	8,9	400 500	0,14738	59 026
10.	pertuzumab	840 mg FTW, 420 mg NTW	18,5	11 760	15,09	177 458

*added expense for TRA
FTW: the first three weeks, NTW: the next three weeks, PFS: progression-free survival, QMPTC: quantity of a medicinal product for therapeutic cycle, RPAP: reference price for the amount of product, AEP: added expense to progression, BGN: Bulgarian Lev

Table 4. Cost-effectiveness of targeted therapies for the treatment of breast cancer in Bulgaria (February 2015)

No.	*Drug*	*AEP, (BGN)*	*AS, months*	*ICER, BGN/month*	*ICER BGN/LYG*
1.	bevacizumab	124 593	+1.7	73 290	879 480
2.	bevacizumab	104 658	–	–	–
3.	trastuzumab	21 176	–	–	–
4.	trastuzumab	44 999	+6.9	6521	78 259
5.	trastuzumab	68 822	+8.5	8097	97 164
6.	lapatinib	33 160	+2.0	16 580	198 960
7.	lapatinib	36 477	–4.6	TRA + CAP is dominant to LAP + CAP	
8.	lapatinib	21 176	+4.5	4705	56 470
9.	lapatinib	59 026	+2.8	21 081	252 972
10.	pertuzumab	177 458	–	–	–

AEP: added expense to progression, AS: added survival, ICER: incremental cost effectiveness ratio, LYG: life-year gained, BGN: Bulgarian Lev

The effectiveness of additional costs for targeted breast cancer therapies for 1 month and 1 LYG are presented in Table 4.

Discussion

Targeted drug therapies for the treatment of breast cancer have a different value for ICER - from 56 470 Bulgarian Levs / LYG to 879 480 Bulgarian Levs / LYG. The development of pharmacotherapeutic recommendations based on therapeutic efficacy and cost-effectiveness requires the adoption of a price ceiling for LYG (QALY), i.e. a margin of cost-effective therapies to be paid for with public funds.

The recommended approach for determining this value is 3-fold increase in GDP per capita.

According to the Bulgarian National Statistics Institute [18] based on population level and GDP in Bulgaria, the estimated threshold for ICER is 32 700 Bulgarian Levs / LYG. If this value is perceived by politicians and health experts, then patients with breast cancer have no possibility to have access to targeted therapies. It is therefore necessary to adopt a consensus compromise value in the range 60,000 Bulgarian Levs / LYG-80,000 Bulgarian Levs / LYG (€ 30,000 / LYG- € 40,000 / LYG), as is the practice in most EU countries.

Analysis of the results for therapeutic efficacy, cost-effectiveness and tradeoffs threshold for ICER leads to the following possible pharmacotherapeutic recommendations in Bulgaria for targeted treatment of breast cancer:

1. Application of bevacizumab in combination with paclitaxel or capecitabine for first line treat-

ment of metastatic breast cancer is cost-ineffective and is not recommended. This finding coincides with the recommendations of NICE for bevacizumab+paclitaxel [19] and bevacizumab+-capecitabine [20].

2. The implementation of trastuzumab as monotherapy or in combination with paclitaxel or docetaxel may be perceived as cost-effective in Bulgaria for adjuvant therapy and first-line treatment of metastatic breast cancer and be recommended in the current pharmacotherapeutic guidelines. This conclusion also coincides with the recommendations of NICE for trastuzumab [21] and trastuzumab+paclitaxel (docetaxel) [22].

3. The implementation of lapatinib in combination with capecitabine, trastuzumab or letrozole as a first-line treatment of metastatic breast cancer is cost-ineffective and is not recommended. This conclusion also coincides with the recommendations of NICE - lapatinib+capecitabine [23], and lapatinib+letrozole [24].

4. The application of pertuzumbab in combination with trastuzumab and docetaxel as first-line treatment of metastatic breast cancer cannot be assessed at this stage because of missing data on OS benefit and inability to calculate the ICER. Despite the positive data on PFS, therapy with pertuzumab + trastuzumab + docetaxel is expected to be cost-ineffective.

The opinion of NICE is similar [25]. The therapy (pertuzunib+trastuzumab+docetaxel) is not recommended until clear evidence of therapeutic and cost-effectiveness is defined.

Conclusion

The current pharmacotherapeutic recommendations for targeted therapies for the treatment of breast cancer are based on evidence of therapeutic efficacy and cost-effectiveness. Their application in therapeutic practice in Bulgaria is necessary to ensure patient access to effective therapies within the limited public funds. It is therefore necessary to make certain adjustments to the medical standards for systemic drug treatment of breast cancer, issued by Bulgarian Oncological Society through national consensus decision in 2015 [4] as follows:

• First-line chemotherapy in patients who received adjuvant anthracyclines: the combination paclitaxel + bevacizumab is not recommended.

• Chemotherapy in patients resistant to taxanes and anthracyclines: the combination capecitabine + bevacizumab is not recommended.

• Systemic therapy in patients with overexpression of HER2: pertuzumab+trastuzumab+docetaxel; trastuzumab+lapatinib; trastuzumab+emtansine; capecitabine+lapatinib; lapatinib+letrozole are not recommended.

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