

THE COST OF ONCOLOGY MEDICINES

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Abstract. *Cancer as a financial value is one of the most expensive diseases. Costs, including the cost of new cancer drugs, are increasing at an unsustainable rate, threatening the permanent access of patients to treatment. Prices for new treatments against cancer have doubled over the past 10 years and now are usually between USD 6000 and USD 10,000 per month, this increase is often not correlated with reimbursement and implemented public health benefits. According to various authors, these results lead to debate whether the cost differences between EU countries and the US for the treatment of oncologic diseases are transformed into improved outcomes for patients, and must also take into account key factors such as lifestyle, late diagnosis, and management approach for treatment, reimbursement of oncology treatment and control of various institutions on spending.*

Key words: *pharmacotherapy cost, oncologic diseases, cancer, treatment*

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INTRODUCTION

At present, cancer is a reason for 12% of all deaths by causes in the world [1]. It is expected to increase the number of deaths from 6 million to 10 million over the next 20 years. Around 20 million people in the world are living with the diagnosis of cancer as their number is expected to reach 30 million by 2020 [11].

Regardless of the global concern, indicators of morbidity and mortality showed at least two-fold differences between the European countries, they are more pronounced in specific locations of cancer. The effect of cancer has certain characteristics and even changes. These changes relate to the cancers, and for a given age group, gender and region. Observed differences in morbidity and mortality are also due to the different approach, measures and control in respect of various factors – exogenous and endogenous, leading to the occurrence of cancer diseases.

They have to comply fully with the demographic processes of population aging globally and its growth, which will lead to an annual increase in the number of patients with cancer over the next 15 years. In the greatest extent, these developments will affect the incidence of the most common cancers, which must be consistent with united action to control them [1].

Cancers historically, but also in personal one, are accepted as devastating and deadly diseases affecting almost all ages, along with a wide range of diagnostic and therapeutic methods. Investments by the pharmaceutical industry and the governments of different countries, especially members of the EU and the USA have multiplied in recent years [12].

According to the American Institute for the study of cancer diseases (AICR), oncology medicines cost USD 895 billion annually, more than any other group of diseases, for example: for cardiovascular disease are spent globally USD 753 billion, for road traffic accidents and diabetes – about USD 204 billion for each

separately [13]. Price for a year of human life is increased from USD 139,100 in 2005 to USD 207,000 in 2013. The biggest financial impact in terms of point of loss of life and productivity occupy oncological diseases, accounting for 1.5% of the global gross domestic product (GDP). According to AICR 11% of these costs are for drug therapy. In 2015 National Bureau for Research and Economic Studies of the USA found that the prices of drugs “cancer” increased by 10% per year between 1995 and 2013.

In 2014, a study [17], published in *The Lancet* found that early treatment with drugs for oncological diseases is often impossible in low-income countries [17]. According to the American Cancer Society (ACS), the factors that determine the oncological treatment are the type of treatment, its duration, the place where it is held and the type of insurance coverage. Therefore, studies of the changes in the cost of oncology pharmacotherapy are necessary to reveal the tendencies and improve peoples’ access to them.

Health insurance patients are the most important factor in the equation of personal health care costs of cancer patients. Insurance plans typically cover the major costs such as hospital stays, tests and procedures, and therapy prescribed by the attending physician. However, the study claimed there is no full coverage and full treatment of the sick and often require some type of additional payment [13].

The goal of this study is to analyze the cost paid by the public funds for oncology medicines in Bulgaria during 2013-2015 and to compare them with the cost in other EU countries.

MATERIAL AND METHODS

It was made literature search in the databases PubMed, Scopus and Google Scholar for the publications that cover the cost of oncology medicines, cost of oncology diseases and the way of their funding in the EU countries. The relevant studies that publish information about the total costs paid by public funds for oncology medicines are included in the analysis.

Then it was collected officially published information about the cost per INN (International Nonproprietary Names) paid for oncology medicines by the National Health Insurance Fund in Bulgaria during 2013-2015 in local currency. The exchange rate was EUR 1 = BGN 1,958.

The changes in the cost were analyzed by calculating the percentage of increase (or decrease) by INN. Changes in cost were tested for statistical significance.

RESULTS

Costs on macro level for cancer patients in member states of the EU

Authors involved with the topic found that of all tested member states – Belgium, England, Estonia, France, Lithuania, the Netherlands, Northern Ireland, Norway and Poland – only four countries (Belgium, England, France and Poland) have estimated the total budget allocation for the implementation of activities, related to the therapy of oncological diseases. In Belgium, EUR 380 million were allocated between 2008 and 2010 for oncology diseases, in England GBP 70 million is allocated to “care cancer patients” every year, and in France 640 million euros have been allocated for cancer care in 2007, in Poland – three million Polish Zloty was allocated for the implementation of a program for cancer in 2006-2015 [14].

Eight of nine countries (except the Netherlands) have made clear statements about the need for additional funding to support the fight against “cancer”. In the Netherlands, the authors noted that the new projects are funded by the redistribution of existing financial resources. Researchers, however, noted that the general lack of budgeting for projects for the treatment of cancer in many countries is alarming. The current financial climate exacerbates this problem, including rising levels of unemployment and rising government deficits [14].

Funding therapy for cancer treatment at the level of national programs in the EU

Authors working in the field investigated 14 members of the EU. In England, the average cost for oncology medicines increased to 60-80 million pounds annually in recent years. In Italy investing in drugs is determined by analysis of costs and benefits, especially in terms of highly expensive innovative medicines [14].

Numerous researchers explored the specific reasons for the increasing costs of therapy of oncological diseases [15]. In the first place, these are high cost and long period of conducting clinical trials from phase 1 to phase 4; secondly, because most cancers are incurable, patients are treated with each approved agent (sequentially or in combination). This creates a virtual monopoly as the use of one drug does not automatically mean that the others are no longer needed. Third, even when the monopoly is broken by the arrival of “new and improved” versions of the approved drugs, the older (in the cases the most generic) drugs tends to be regarded as already unsuitable for therapy, thereby actually the cost even increases because the price of new, innovative medicines, and “monopoly of new drugs” remains. Fourth, the very

nature of cancer diseases and severity of diagnosis play a role in patients and physicians who often are willing to pay the high cost of treatment even for minor improvements in outcome. Finally, the authors note that agencies such as the FDA, and EMA (European Medicines Agency), approving and authorizing the use of new products, as well as national councils makers for reimbursement of appropriate drugs, especially based on HTA (health technology assessment), cannot take their decisions solely on the basis of economic efficiency, without noting even psychological efficiency [16].

Reimbursement approach in Bulgaria

The National Health Strategy for the period 2008-2013 by Strategic Objective I: Ensuring conditions for health promotion and disease prevention provided in section 4.2 Development and implementation of programs for socially significant diseases and health problems representing national priorities (incl. Oncology diseases).

According to the National Framework Agreement between the National Health Insurance Fund and the Bulgarian Physicians' Union and the Union of Dentists in Bulgaria, cancer is included in the group of socially and priority for the country diseases [3].

There is a national strategy for prophylactic cancer screening (including cervical cancer), the schedules work program for the period 2001-2006 [4]. In the opinion of many experts, this program is not carried out according to its vision.

In December 2007, the 40th National Assembly established group "Parliamentary consensus on combating major diseases". The group is taking a number of actions and initiatives held a series of meetings and roundtables for the identification and possible solutions to major problems in the field of oncological diseases with the participation of leading experts in this field, including national and Republican consultants, non-government organizations and patient organizations, representatives of Presidency, Council of Ministers and the National Health Insurance Fund [4].

On June 12th, 2008, 40th National Assembly of the Republic of Bulgaria adopted unanimously statement in support of actions to limit and control of oncological diseases in Bulgaria. In pursuance of the Declaration of the National Assembly a working group to develop a national anti-cancer program and the National anti-cancer plan was set. In this connection it is prepared a National Program for Prevention and Control of Cancer in Bulgaria 2009-2018 and Plan for strategy, prevention and control of cancer in the Republic of

Bulgaria for the period 2009-2018 [6, 7]. The two documents are not validated. Therefore, the leadership of the Ministry of Health decided at that time a working group with the participation of patients' organizations to draw up to a national program to fight cancer in the Republic of Bulgaria up to February 15, 2010, then it should be presented to the Council of Ministers.

Currently, there is no functioning national program to fight cancer. Against this background, the measures to reduce the cost of cancer drugs are sporadic and unsystematic [10]. The amendments to Regulation 40, effective from 1 January 2014 [8], introduce the restriction that the innovative oncology products have to be included in the PDL (Positive List of Drugs) annually, thereafter, NHIF (National Health Insurance Fund) pays oncology products for the oral treatment not only in Annex 1 to the PDL but also in Annex 2 outside clinical paths even in recent years – 2014, 2015. In 2016 it is negotiated a separate sum of oncology products in the context of the total amount contained in a contract between the NHIF and the Medical Association

Evidenced by the report of NHIF from June 2015 to the ongoing implementation of the budget of the NHIF for medicines, the expected shortfall at the end of 2015 for drugs, medical devices and foods for special dietary purposes is going to be BGN 67 468 000 and for medicines to treat cancer in terms of hospital care BGN 54 469 000. Such forecasts are made based on the rising average monthly expenditure in 2015 [9].

Although widely proclaimed measures to reduce the cost of drugs, including for cancer, the upward trend remained in each subsequent year (Table 1).

DISCUSSION

According to the international statistics on morbidity and mortality, the cancer frequency increases. In particular, in Bulgaria in 2013 (the latest published data) 10 neoplasms are the second leading causes of mortality 251.5 per hundred thousand population as male mortality remains much higher than in women. The incidence of malignant neoplasms also tends to increase [10].

In 2013, the incidence of malignant neoplasms increased compared to the previous year to 461.9 per hundred thousand inhabitants. These data indicate that regardless of the continually rising costs for the therapy of these disorders, yet those costs do not lead to effective results, both in terms of incidence, where the main factor is the prevention and in terms of reducing the death rate from cancer [1, 10].

Table 1. Changes in costs of anticancer drugs by INN during 2013-2015

ATC Anatomical Therapeutic Chemical (ATC) Classification System	INN International Non-proprietary Name	Reimbursement amount		Reimbursement amount		%	Reimbursement amount		%
		2013 (BGN)	2014 (BGN)	2014 (BGN)	2015 (BGN)		2015 (BGN)	Change 2015-2014	
B02BX04	Romiplostim	2 180 507	3 613 386		3 546 956	65.71		-1.84	
B02BX05	Eltrombopag		482 495		1 353 060			180.43	
B03XA01	Epoetin alfa	497 968	555 537		809 341	11.56		45.69	
B03XA02	darbepoetin alfa	823 358	1 839 244		2 385 113	123.38		29.68	
H01CB02	Octreotide	1 814 733	2 326 564		2 864 583	28.2		23.13	
H02AB02	Dexamethasone	161 075	180 249		152 520	11.9		-15.38	
J06BA02	Human normal immunoglobulin		853		99 004			11506.54	
L01AA01	Cyclophosphamide	225 670	426 410		477 371	88.95		11.95	
L01AA06	Ifosfamide	856 355	751 247		639 603	-12.27		-14.86	
L01AA09	Bendamustine hydrochloride	448 147	1 600 976		1 528 894	257.24		-4.50	
L01AD01	Carmustine	94 907	7 712			-91.87			
L01AX03	Temozolomide	1 355 561	869 946		576 155	-35.82		-33.77	
L01AX04	Dacarbazine	95 833	196 953		148 548	105.52		-24.58	
L01BA04	Pemetrexed	4 938 591	6 128 684		6 289 160	24.1		2.62	
L01BB04	Cladribine	109 287	123 257		94 506	12.78		-23.33	
L01BB05	Fludarabine phosphate	363 890	173 328		80 348	-52.37		-53.64	
L01BB06	Clofarabine	1 480 355	3 155 392		1 409 559	113.15		-55.33	
L01BB07	Nelarabine	15 509	41 663		18 602	168.64		-55.35	
L01BC01	Cytarabine	296 287	252 395		233 222	-14.81		-7.60	
L01BC02	5-Fluorouracil	172 892	279 215		372 672	61.5		33.47	
L01BC05	Gemcitabine	808 322	631 101		437 110	-21.92		-30.74	
L01BC06	Capecitabine	5 661 043	1 502 032		520 052	-73.47		-65.38	
L01BC53	tegafur/gimeracil/oteracil		40 273		141 826			252.16	
L01CA01	Vinblastine	43 845	45 510		35 311	3.8		-22.41	
L01CA02	Vincristine	80 238	82 300		80 619	2.57		-2.04	
L01CA04	Vinorelbine	216 659	258 716		210 825	19.41		-18.51	
L01CB01	Etoposide	167 086	200 364		171 375	19.92		-14.47	

L01CD01	Paclitaxel	659 915	686 126	3.97	708 961	3.33
L01CD02	Docetaxel	1 015 659	664 832	-34.54	422 069	-36.52
L01CD04	Cabazitaxel	195 113	3 180 139	1529.9	3 575 013	12.42
L01CX01	Trabectedin	38 804	194 573	401.43	58 726	-69.82
L01DB01	Doxorubicin hydrochloride	141 244	2 658 736	1782.37	2 820 322	6.08
L01DB03	Epirubicin	1 223 096	1 555 758	27.2	1 276 881	-17.93
L01DB06	Idarubicin	123 593	99 900	-19.17	96 297	-3.61
L01DB07	Mitoxantrone	116 718	39 650	-66.03	28 109	-29.11
L01DC01	Bleomycin	3 572		-100		
L01DC03	Mitomycin	334 570	488 904	46.13	710 189	45.26
L01XA01	Cisplatin	386 109	327 168	-15.27	272 224	-16.79
L01XA02	Carboplatin	390 790	651 780	66.79	689 064	5.72
L01XA03	Oxaliplatin	448 271	648 857	44.75	569 332	-12.26
L01XC02	Rituximab	8 664 629	9 564 990	10.39	9 289 457	-2.88
L01XC03	Trastuzumab	25 699 416	28 066 820	9.21	32 546 543	15.96
L01XC06	Cetuximab	2 848 279	5 850 361	105.4	7 257 980	24.06
L01XC07	Bevacizumab	22 525 111	32 364 113	43.68	38 507 474	18.98
L01XC08	Panitumumab	3 809 878	5 565 627	46.08	6 125 504	10.06
L01XC11	Ipilimumab		279 395		2 028 747	626.12
L01XE01	Imatinib	12 704 549	9 963 545	-21.57	8 180 949	-17.89
L01XE02	Gefitinib	2 069 502	2 290 891	10.7	1 958 207	-14.52
L01XE03	Erlotinib	5 102 917	6 959 394	36.38	7 879 221	13.22
L01XE04	Sunitinib	6 158 380	7 302 621	18.58	7 231 135	-0.98
L01XE05	Sorafenib	4 672 199	5 547 446	18.73	6 700 361	20.78
L01XE06	Dasatinib	2 581 825	2 829 186	9.58	2 749 638	-2.81
L01XE07	Lapatinib	2 323 999	3 085 399	32.76	2 777 618	-9.98
L01XE08	Nilotinib	11 001 962	13 237 985	20.32	14 743 802	11.37
L01XE09	Temsirolimus	306 250	298 199	-2.63	488 953	63.97
L01XE10	Everolimus	2 011 974	5 101 729	153.57	7 594 149	48.85
L01XE11	Pazopanib	5 636 484	7 478 311	32.68	5 720 180	-23.51
L01XE15	Vemurafenib		3 194 221		6 897 567	115.94
L01XX17	Topotecan	140 322	131 691	-6.15	68 273	-48.16

L01XX19	Irinotecan	348 242	322 983	-7.25	348 446	7.88
L01XX23	Mitotane	18 697	42 828	129.06	32 429	-24.28
L01XX32	Bortezomib	6 097 113	7 077 786	16.08	6 702 857	-5.30
L01XX41	Eribulin		488 172		1 254 076	156.89
L02BX03	Abiraterone acetate	176 400	6 421 158	3540.11	9 589 684	49.35
L03AA02	Filgrastim	960 923	837 813	-12.81	934 433	11.53
L03AA10	Lenograstim	111 090	114 057	2.67	48 491	-57.49
L03AA13	Pegfilgrastim	3 563 803	5 220 313	46.48	5 814 623	11.38
L03AB04	Interferon alfa-2a	307 695	287 264	-6.64	404 878	40.94
L03AX03	Mycobacterium bovis BCG (Bacillus Calmette – Guérin)	152 519	224 684	47.32	143 958	-35.93
L03AX16	Plerixafor	24 901	22 978	-7.72		
L04AD01	Ciclosporin	15 894	24 078	51.49	13 848	-42.49
L04AX03	Methotrexate	74 157	56 269	-24.12	47 098	-16.30
M05BA03	Pamidronate	933 352	367 570	-60.62	110 509	-69.94
M05BA06	Ibandronate	649 288	121 782	-81.24	32 506	-73.31
M05BA08	Zoledronic acid	8 983 283	2 171 856	-75.82	394 128	-81.85
M05BX04	Denosumab	723 940	4 727 351	553	7 377 856	56.07
N02AA01	Morphine	281 291	217 624	-22.63	171 323	-21.28
N02AA05	Oxycodone	1 019 936	928 742	-8.94	633 232	-31.82
N02AA08	Dihydrocodeine	183 932	115 646	-37.13	74 472	-35.60
N02AA55	Oxycodone hydrochloride/ Naloxone hydrochloride	891 602	1 041 655	16.83	1 185 980	13.86
N02AB02	Pethidine hydrochloride	342	2 747	703.22	5 755	109.50
N02AB03	Fentanyl	104 639	187 758	79.43	222 524	18.52
N02AE01	Buprenorphine		29 889		176 206	489.53
N02AX02	Tramadol	60 367	59 825	-0.9	55 351	-7.48
V03AF03	Calcium folinate	515 297	683 945	32.73	1 029 854	50.58
V04CJ01	Thyrotropin alfa	1 528	4 585	200.07		
	Total	172 443 477	217 877 517	26.35	248 472 833	14.04

* Source: Digital data on costs: National Health Insurance Fund

Table 2. Descriptive statistics of oncoterapy costs 2013-2014

N = 80	Mean (SD)	Median	Mode	Standard error	Min/Max
Oncoterapy costs	126.25 (± 478.23)	17.70	-100.0	53.56	-100.00 /3540.11

Table 2 illustrates these statistical data for the period 2013-2014 in Table 1 and includes arithmetic average, minimum and maximum ones, standard error and standard deviation. It is important to know that information distribution is not normal, because the statistical dimensions such as notions have different values on a large scale. This is visible below in Histogram (Figure 1). This is not a problem for the analysis

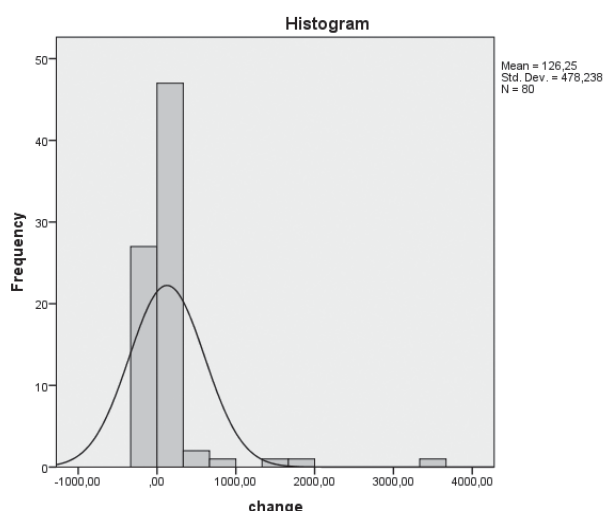


Fig. 1. Frequency distribution of the costs of oncoterapy of NHIF 2013-2014 – Change

All exported data here provoke several important questions: The National Cancer Registry publishes information on morbidity and mortality with a delay of at least two years of data.

There are no patient registries of the patients with cancer. The lack of such a database determines the impossibility of real forecast budget for medicines for treating of cancer diseases.

Last but not least, it is the question of the adequacy of control by the Public Fund on spending of cancer drugs and the increased in recent years parallel exports of such drugs [18].

It should be noted, however, the mere fact that access of Bulgarian patients to new, innovative drugs for the treatment of cancer is improved, although it is

because the Figure 1 only shows the distribution of information according to their frequency. (Conclusions will apply to the sample, but cannot summarize cases beyond. When dealing with cancer diseases or extracts from non-randomized patients as well in this case, such graphics are possible.)

In a similar way, the descriptions of Figure 2 and Table 3 are following.

Table 3. Descriptive statistics of the costs of oncoterapy of NHIF 2014-2015

N = 82	Mean (SD)	Median	Mode	Standard error	Min/Max
Oncoterapy costs	157.19 (± 1272.86)	-2.845	-81.85	140.56	-81.85 /11506.54

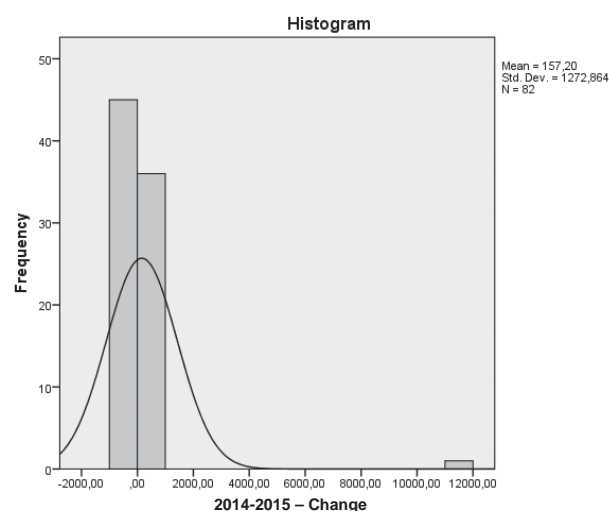


Fig. 2. Frequency distribution of the costs of oncoterapy of NHIF 2014-2015 – Change

once a year, subject to the regulatory framework [8], these new products are included in the PLD and are reimbursed by the NHIF.

CONCLUSION

These data showed that the cost of oncoterapy in Bulgaria followed the global upward trend, but the percentage on an annual basis is higher than average for developed countries.

According to these data, the progressive trend of the cost of almost all surveyed INN remains.

The reasons are probably due to better prevention and diagnosis, but in a relatively fixed number of patients an extremely high rate of change in the di-

rection of increasing costs of the oncotherapy in our country is seen.

Specifying the actual causes requires control and analysis of specialized hospitals for oncology therapy, which number has also risen in recent years, particularly in the larger and more economically developed cities, as well as the effectiveness of the schemes and dosage regimens of oncology drugs.

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