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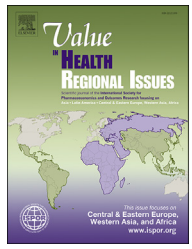

Preference-Based Assessments

What Is the Value of Innovative Pharmaceutical Therapies in Oncology and Hematology? A Willingness-to-Pay Study in Bulgaria

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ABSTRACT

Objectives: To analyze the views of Bulgarian oncologists and hematologists regarding the value of innovative pharmaceutical treatments in their clinical area. **Methods:** Physicians were invited to review a life-prolonging scenario and to indicate what minimum improvement in median survival a new treatment would have to generate for them to recommend it over the standard of care. Respondents were also asked to state the highest cost at which they would recommend a new therapy that would improve patient's health-related quality of life (HRQoL) but would have no impact on survival. In addition, physicians were asked whether they would consider different responses under certain circumstances. Responses were used to calculate incremental cost-effectiveness ratios (ICERs) for each scenario. **Results:** In the life-prolonging scenario, participants required a median of 12-month improvement in the survival to reimburse a new therapy at an incremental cost of €50 000, implying a willingness-to-pay of €50 000 per QALY gained. In the HRQoL-enhancing scenario, respondents indicated a €100 000 median cost per QALY gained. We observed a significant variation in responses. Although the median ICER for better HRQoL was twice as high as the median ICER for longer survival, 5% trimmed mean values were almost equal. Physicians did not believe that a higher ICER should be used for the treatment of children or for rare diseases. **Conclusions:** We found a high willingness-to-pay for innovative drugs in oncology and hematology. The wide range of responses observed, however, indirectly implies a lack of consensus on the use of explicit ICER thresholds in Bulgaria.

Keywords: Bulgaria, cancer, cancer premium, cost-effectiveness, willingness-to-pay

Introduction

Innovative pharmaceutical therapies in oncology and hematology have been heavily scrutinized over the last decade. Spending on these treatments has risen dramatically compared with other clinical areas. This issue has triggered a prolonged debate on the high cost and relative value of new cancer interventions.[1] Addressing it requires difficult trade-offs between cost, harms, and ability to benefit when using limited public resources.[2] Societal preferences and public concerns further complicate the process of assessing the value of new anticancer treatments.

Health technology assessment (HTA) is the common approach to inform public coverage and reimbursement decisions. One of the major purposes of HTA is to assess whether an intervention provides a good value for money. For this aim, an economic evaluation that weighs clinical and economic evidence and combines these considerations into an incremental cost-effectiveness ratio (ICER) is conducted. Review of cost per quality-adjusted life-year (QALY) gained and application of ICER thresholds have been discussed as a way to enhance consistency and transparency of the decision-making process and to reduce the burden of responsibility on decision makers.[3] Despite these theoretical advantages, few jurisdictions have undertaken measures to implement explicit ICER thresholds. Stakeholders feel uncomfortable with denying reimbursement of any intervention purely on the basis of an ICER exceeding a specific threshold. Rather, ICER

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is considered as one element in the reimbursement decision-making process, together with other disease- and treatment-specific criteria.[4,5]

Previous studies have shown that new cancer therapies tend to benefit from such supplementary considerations. For example, HTA agencies often accept a higher value of cost per QALY gained when a treatment is aimed at prolonging survival for patients with a short expected remaining life-expectancy, the so-called end-of-life premium.[6] Some jurisdictions have secured specific funds to reimburse innovative cancer medicinal products, such as the Cancer Drugs Fund (CDF) in the UK. The CDF is currently providing access to medicinal therapies in cases where more data are needed for a robust estimation of real-world effectiveness and cost-effectiveness by the National Institute for Health and Care Excellence (NICE).[7]

In Bulgaria, reimbursement of innovative medicinal therapies has led to a continuous deficit spending.[8] Various tools have been suggested to tackle this problem with no sustainable solutions yet. In 2017, legislators even adopted a 1-year ban on reimbursement of new medicinal products by the National Health Insurance Fund (NHIF), a move that was subsequently reversed because of public pressure.[9] Although there is no explicit ICER threshold used by Bulgarian regulators, this example illustrated the conflict between the different perceptions and valuations of innovative treatments. Although health authorities and payers seem to be more interested in cost and budget impact, the public and patient organizations in particular demonstrate a great concern about health inequalities and access to treatment. Such findings are neither controversial nor novel. Various studies have confirmed disagreements in willingness-to-pay among different stakeholders.[1,2,10-21]

Eliciting willingness-to-pay for innovative anticancer treatments is critical for promoting accountability for reasonableness in coverage and reimbursement decisions and for designing market access strategies for new drugs. In this context, no formal willingness-to-pay studies on innovative medicinal therapies in oncology and hematology have been conducted in Bulgaria. Whereas regulators and payers have the formal prerogative power on pricing and reimbursement, little is known on the opinions and attitudes of health professionals in this field.[1] Judgments of oncologists and hematologists may assist decision makers in their deliberations on coverage and reimbursement of new and innovative medicinal therapies.[10]

Objective

The aim of this study was to analyze the views of Bulgarian oncologists and hematologists regarding the value of innovative medicinal treatments in their clinical area. In particular, we compared valuation of life-prolongation and health-related quality-of-life (HRQoL)—enhancing outcomes attributable to new pharmaceuticals.

Methods

Study Design

The study design was based on a previous research conducted in Israel,[11] the United States, and Canada.[1,12,15] The survey consisted of 19 questions. Each question contained a free text field for providing additional information, if desired. The survey was piloted among a small group of health professionals for their input on the questionnaire's clarity. The study was conducted in Bulgaria through an online survey in May to July, 2018.

Each participant was asked to consider 2 hypothetical clinical scenarios. First, respondents were requested to review a life-prolonging case involving a patient with metastatic cancer expected to survive 12 months with a standard medical treatment at an annual cost of €25 000. Then, participants were presented with a scenario describing a new medicinal therapy at a total cost of €75 000. HRQoL outcomes were assumed to be similar in both treatment options. Physicians were asked to indicate what minimum improvement in median survival (in terms of months of survival gained) the new treatment would have to generate for them to recommend it over the standard of care (Fig. 1).

The HRQoL-enhancing scenario involved a second patient with metastatic cancer, expected to survive 12 months with a standard medical treatment at an annual cost of €25 000. HRQoL of this patient was 50 on a 0 to 100 scale (where 0 represents the worst possible HRQoL and 100 the best possible HRQoL) (Fig. 2). Then, respondents were requested to state the highest cost at which they would recommend a new medicinal therapy that would improve patient's HRQoL from 50 to 75 but would have no impact on survival. In both scenarios, respondents were asked to assume that patients do not bear any cost or copayment for the treatment and medications are fully reimbursed by public funds.

After each valuation question, participants were asked whether they would alter their response if the new medicinal product is indicated for children or for rare diseases. Responses were used to assess the acceptance of higher ICERs under these specific circumstances.

Ethical approval was not required for this study in accordance with the national and institutional guidelines. From a methodological point of view, the survey was sociological, with no clinical research. No personal data were saved or analyzed.

Study Participants

A convenience sample was compiled on the basis of the Bulgarian Cancer Scientific Society, the Bulgarian Association of Medical

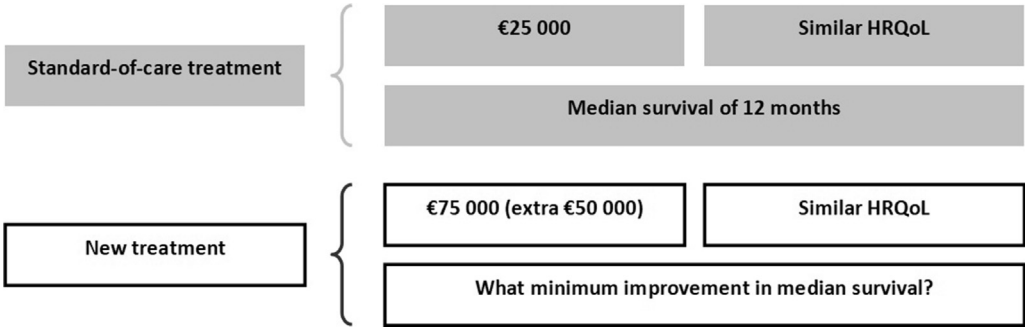

Fig. 1 – Presentation of the life-prolonging scenario studied.

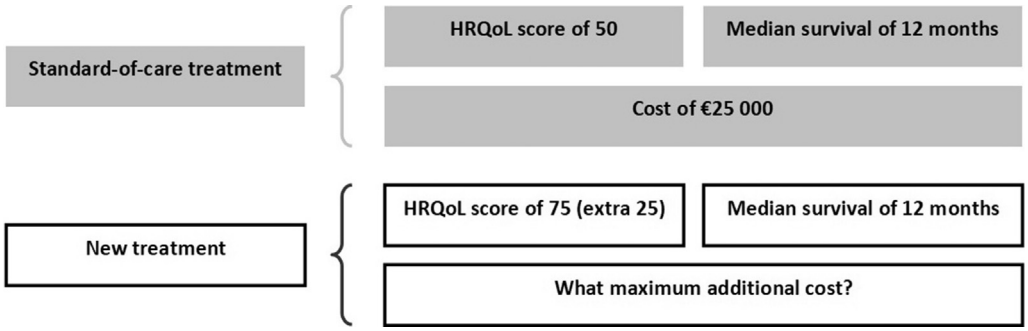

Fig. 2 – Presentation of the health-related quality of life–enhancing scenario studied.

Oncology, and the Bulgarian Medical Society of Hematology, as well as from healthcare providers in the field of oncology and hematology. A total of 230 physicians with publicly available email addresses were identified. They were contacted by email and asked to participate in the survey with an invitation letter describing the study. No incentives for participation were provided. The survey questionnaire was developed and distributed using LimeSurvey (version 2.72.6+171207; LimeSurvey, GmbH, Hamburg, Germany).

Data Analysis

ICER (average incremental cost in euros associated with one additional QALY gained) was the primary outcome measure of the reviewed scenarios. Participants' responses were used to calculate ICER for the 2 patient scenarios presented. For the life-prolongation scenario, the values were calculated as follows:

$$ICER = \frac{EUR\ 50\,000}{Number\ of\ months\ of\ additional\ survival} \times 12\ months$$

For example, a respondent who indicated a 3-month minimum improvement in median survival needed to recommend a treatment at an incremental cost of €50 000 implicitly endorsed an ICER of €200 000 per QALY gained ([€50 000/3] × 12 = €200 000).

In the HRQoL-enhancing scenario, the new treatment increases the patient's HRQoL by 25 points over the standard of care, thus providing one quarter of a QALY. The ICER values were calculated as follows:

$$ICER = \frac{Incremental\ \ cost\ of\ treatment}{0.25\ QALY}$$

For example, a physician who said that she or he would recommend the new treatment at an additional cost of €50 000 implied an ICER of €200 000 per QALY gained (€50 000/0.25 = €200 000).

Because data for the ICER were not normally distributed, 5% trimmed mean and median values were used. These measures are appropriate in such cases because they are less sensitive to outliers and provide a more valid estimate of mean values. We used the Kruskal–Wallis H test to assess the differences in oncologists' and hematologists' implied ICER thresholds. Statistical significance was considered if the P-value was less than .05. Chi-square, Fisher exact tests, and one-way ANOVA were used to compare the studied groups in terms of main sociodemographic characteristics. Data were analyzed using SPSS (version 11.5; SPSS, Inc., Chicago, IL, USA).

Results

Profile of Survey Respondents

In total, 70 of 230 invited participants completed the survey with an overall response rate of 30.4%. Seven respondents indicated none or a medical specialty outside of the field of oncology and hematology, so they were excluded from further analyses. The final sample included 29 oncologists, 23 hematologists, 6 pediatric oncohematologists, and 5 physicians having specialties in both oncology and hematology (Table 1). The latter 2 categories were classified as a single group of oncohematologists. The mean age of survey respondents was 50.5 years. Female participants (55.6%) slightly predominated. The mean professional experience was approximately 25 years, with oncohematologists having practiced longer than the other 2 groups. The majority of the responding physicians worked in the public sector.

Incremental Cost-Effectiveness Ratios

In the life-prolonging scenario, survey participants required a median of 12-month improvement in the survival to reimburse a new therapy at an incremental cost of €50 000. This resulted in a €50 000 median cost per QALY gained (Table 2). The 5% trimmed mean ICER was €96 186. Oncologists requested the lowest minimum survival (a median value of 6 months), thus implying the highest median ICER (€100 000). These differences were not statistically significant, but they showed a wide range of opinions even within individual respondent categories.

In the HRQoL-enhancing scenario, physicians indicated a €100 000 median cost per QALY gained, whereas the 5% trimmed mean ICER was €93 500 (Table 2). Oncohematologists provided the most conservative estimate for this indicator, with a €40 000 median cost per QALY gained and a 5% trimmed mean ICER of €54 286, but the difference was not statistically significant. Comparing the 2 scenarios, the median ICER for better HRQoL was twice as high as the median ICER for longer survival. Nevertheless, these ICERs were almost equal when looking at the 5% trimmed mean values, with the ICER for longer survival even being slightly higher.

Special Considerations

Survey respondents did not support the use of special considerations to accept higher ICERs (Table 2). Rare disease indication as a modifying criterion in decision making was only endorsed by approximately 20% of physicians in both scenarios. Pediatric indication was more positively seen as a special consideration. Nevertheless, respondents still rejected its use as a reason for

Table 1 – Profile of survey respondents.

	Total (n = 63)	Oncologists (n = 29)	Hematologists (n = 23)	Oncohematologists (n = 11)	P
Age in years, mean ± SD	50.5 ± 11.3	52.0 ± 10.5	47.2 ± 10.4	53.1 ± 14.4	>.05
Sex, % (n)					
Male	44.4 (28)	41.4 (12)	47.8 (11)	45.5 (5)	>.05
Female	55.6 (35)	58.6 (17)	52.2 (12)	54.5 (6)	
Professional experience in years, mean ± SD	25.2 ± 11.5	26.5 ± 10.4	20.9 ± 10.8	30.8 ± 13.3	.042
Main professional role, % (n)					
Diagnosis and treatment	98.4 (62)	100 (29)	95.7 (22)	100 (11)	>.05
Administration	1.6 (1)	—	4.3 (1)	—	
University hospital experience, % (n)					
Yes	77.8 (49)	72.4 (21)	78.3 (18)	90.9 (10)	>.05
No	22.2 (14)	27.6 (8)	21.7 (5)	9.1 (1)	
Sector (>50% of the time), % (n)					
Public	76.2 (48)	72.4 (21)	73.9 (17)	90.9 (10)	>.05
Private	9.5 (6)	13.8 (4)	8.7 (2)	—	
Equally	14.3 (9)	13.8 (4)	17.4 (4)	9.1 (1)	

SD indicates standard deviation.

accepting higher ICERs. The majority of responders in both scenarios were against this consideration (58.7% in the life-prolonging scenario and 61.9% in the HRQoL-enhancing scenario).

Discussion

No Explicit ICER Threshold?

We found high ICER thresholds for innovative medicinal therapies in oncology and hematology. These values are in line with results from previous studies.[11-13] The wide range of responses, however, indirectly implies a lack of consensus on the use of explicit ICER thresholds in Bulgaria. The concept of ICER does have important advantages for decision makers, and in previous studies oncologists supported the use of cost-effectiveness data in coverage and reimbursement decisions.[10,15,22] Still, explicit ICER thresholds remain a politically and morally sensitive issue. Researchers agree that there is no such thing as a constant, context-independent willingness-to-pay for any QALY unit gained.[23] Not applying explicit thresholds allows for more flexible deliberations and may be more attractive to decision makers.[3]

Previous studies generally found that health professionals value prolonged survival more than enhanced HRQoL.[11-13] Although the median ICER for better HRQoL was twice as high as the median ICER for longer survival in our study, 5% trimmed mean values were almost equal. In this context, we could conclude that these 2 components of health outcomes are more or less equally appraised by Bulgarian oncologists and hematologists. Despite continuous improvement in diagnosis and treatment of this disease, cancer becomes chronic in many patients.[24] Quality of life is a substantial issue and some studies even suggest that patients may value improved HRQoL more than increased survival.[13]

Table 2 – Cost per QALY implied.

	Total (n = 63)	Oncologists (n = 29)	Hematologists (n = 23)	Oncohematologists (n = 11)	P
Life-prolonging scenario					
Minimum number of months, mean ± SD	14.1 ± 11.7	10.4 ± 8.6	19.1 ± 14.3	13.6 ± 10.1	>.05
Minimum number of months, median (range)	12 (1-48)	6 (1-36)	12 (1-48)	12 (6-36)	
Cost/QALY implied (€), median	50 000	100 000	50 000	50 000	
Cost/QALY implied (€), 5% trimmed mean	96 186	117 397	102 550	65 152	.036
Would you accept a higher ICER if the therapy is indicated for children?, % (n)	No 58.7 (37)	No 58.6 (17)	No 56.5 (13)	No 63.6 (7)	>.05
Would you accept a higher ICER if the therapy is indicated for rare diseases?, % (n)	No 82.5 (52)	No 72.4 (21)	No 95.7 (22)	No 81.8 (9)	>.05
HRQoL-enhancing scenario					
Cost/QALY implied (€), median	100 000	100 000	100 000	40 000	
Cost/QALY implied (€), 5% trimmed mean	93 500	107 500	102 105	54 286	>.05
Would you accept a higher ICER if the therapy is indicated for children?, % (n)	No 61.9 (39)	No 58.6 (17)	No 69.6 (16)	No 54.5 (6)	>.05
Would you accept a higher ICER if the therapy is indicated for rare diseases?, % (n)	No 79.4 (50)	No 79.3 (23)	No 73.9 (17)	No 90.9 (10)	>.05

HRQoL indicates health-related quality of life; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Reimbursement decisions should reflect perspectives of different stakeholders. Cost per QALY gained is an important indicator, but real-life implications for patients are even more important. Certainly, ICERs of many innovative therapies are high. Nevertheless, if these medicinal products are effective, even in a very small population, decision makers should consider establishing schemes to allow patient access to these treatments.[25] Generating real-world data from clinical practice allows for price negotiation, adjustment in cost-effectiveness ratios, and performance-based reimbursement. This rationale explains the increasing interest in risk-sharing and managed-entry agreements in the last decade.[26-29] These tools could balance access to innovative therapies against priorities and resources of the healthcare systems.[8]

ICER and Innovative Drugs?

Innovation is the core of modern-day healthcare. Innovative therapies are generally newly introduced or modified health technologies with unproven effects or side effects, undertaken in the best interest of patients.[30] Decision making for coverage and reimbursement of innovative anticancer treatments tends to be one of the most resource-consuming tasks for national health systems and payers.[8,13] This is especially the case of novel and often very expensive medicines offering limited health benefit in advanced disease patients. A study in such settings found that oncologists expected only a half of their patients to derive some clinical benefit from the prescribed treatment. Furthermore, factors influencing clinical decisions were often applied inconsistently and could even contradict published data.[31] In a similar scenario, another study reported patients showing low price elasticity and high willingness to endure side effects despite very small or no survival gains at all.[14]

Innovation does come at a certain price. It is important, however, to understand and appraise the difference between real-world improvement of health outcomes and limited data from clinical trials. Access to new anticancer medicinal products has been hindered by high prices and lack of rigorous evidence on clinical effectiveness. From a payer perspective, significant extra costs should be linked to important health gains.[9] An analysis of cancer drug approvals by the European Medicines Agency (EMA) found that most medicinal therapies were market approved without evidence of benefit on survival or HRQoL. Three years after market entry, evidence was still inconclusive or showing marginal health benefits.[32]

Cost-effectiveness considerations often play a role in negative coverage and reimbursement decisions, but other factors influence these decisions as well.[29] What matters most for regulators, payers, and healthcare providers is how well the new treatment performs in clinical practice in relation to existing therapeutic alternatives.[33] Real-world data are more and more important as the pathways for introduction of new anticancer medicines change and the number of treatment options multiplies. Moen et al. pointed out 3 domains where real-world evidence is critical: validation of surrogate endpoints impact, evaluation of outcomes outside the clinical trial protocols, and optimization of value assessment.[34]

A Cancer Premium, But No Further Exceptions?

HTA is used to inform public reimbursement of new treatments based on additional health generated and cost incurred. The discussion as to whether cancer is worthy of special consideration extends further beyond. A recent review concluded that this debate tends more to be on the value of reducing the total number of deaths from cancer rather than the value of improving the health of cancer patients.[21] Cancer is considered a dread disease and anticancer treatments are being appraised from a different angle. The acceptance of higher ICER thresholds and the establishment of the CDF are assumed to reflect social perceptions of cancer and preferences for increased resource allocation.[35] Nevertheless, the evidence available for a higher public willingness-to-pay for cancer therapies is mixed.[11,21] A large survey in the UK found no explicit support for the end-of-life premium or the prioritization of children or disadvantaged populations as specified by National Institute for Health and Care Excellence. Participants in this study did not support the special funding status for treatments of rare diseases or the CDF as well.[35]

Our study findings present similar results. Surprisingly, even the subgroup of oncohematologists, which included a number of pediatric oncohematologists, rejected the prioritization of children as a reason for accepting higher ICERs. This has important implications for decision makers. Policies introduced on the basis of perceived, but not actual, societal views may mislead priority setting and resource allocation with the potential for significant population health and economic consequences.[35] Nevertheless, support for cancer premium in Bulgaria cannot be fully discarded based on our research. First, we found a high level of willingness-to-pay for innovative drugs in oncology and hematology. Second, we assessed the support for special considerations within the cancer premium, but not the support for the premium itself.

Study Limitations

Our study has several limitations. First, the sample size and response rate may be small compared with previous surveys. Nevertheless, study respondents demonstrated high professional experience and academic background, thus being the clinical experts that are most likely to be involved in reimbursement decisions. Second, HTA and appraisal include a variety of perspectives and stakeholders. Health professionals are only one of these groups, but they offer a unique point of view as they have both healthcare and clinical research experience. Most importantly, they are very often the linking point between patients and payers, thus understanding the legitimate concerns of those parties.

Finally, we used 2 scenarios presenting either life-prolonging or HRQoL-enhancing cases. These are, of course, rather simplistic. Real-world scenarios may combine both life expectancy and HRQoL gains. We separated these components of health outcomes to assess if one of them is more highly appraised. Furthermore, there is one significant factor that plays an important role in reimbursement decision making. New medicinal therapies are very often subject of different discount and rebates agreements, which are kept confidential. These provisions modify ICERs in practice. Discount and rebate negotiations lead to what may be seen as an acceptance of higher cost-effectiveness thresholds, whereas actual treatment cost remains unknown to the public.

Conclusions

We found very high ICER thresholds for innovative therapies in oncology and hematology in our study. The wide range of responses observed, however, indirectly implies a lack of consensus among clinicians on the use of explicit ICER thresholds in Bulgaria. This seems logical in light of all previous research in this field. ICER itself may be an attractive measure, but current practice regards it more as a support tool in decision making. In the context of innovative therapies, ICER may be considered as a starting point for deliberations on other decision-making criteria and price negotiations.

Debate on coverage of new cancer treatments extends beyond economic evaluation and HTA. Cancer premium does exist in one way or another, but the evidence available of higher willingness-to-pay for these therapies is mixed. Therefore, more research is needed to better understand societal needs and expectations, especially patient preferences. Priority setting and resource allocation in healthcare should be based on actual, not assumed, public views. Otherwise, this could have the potential for significant population health and economic consequences.

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