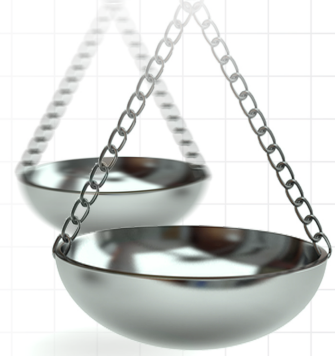
Preliminary communication



Journal of Comparative Effectiveness Research

Should clinically meaningful outcomes in cancer be based on individual survival rather than median overall survival?

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Aim: To assess whether the use of median overall survival to define clinically meaningful outcomes in the area of oncology could yield different decisions compared with those obtained with a more realistic measure such as individual survival. **Methods:** Two scenarios that offered equivalent health gains/money spent were presented: 'median overall survival' scenario (new treatment provided small clinical benefits for the average population) and 'individual survival'scenario (new treatment provided substantial clinical benefits for a small percentage of the patients and no benefits for the rest). Responses from both scenarios were compared. **Results:** Responses between the two scenarios were different for oncologists, healthcare policy makers and patients ($p < 0.05$). 'Individual survival' scenario obtained higher percentage of positive answers compared with 'median overall survival'. **Conclusion:** Expressing the benefits of new oncologic treatments in terms of 'individual survival' may yield to different healthcare decisions compared with the widely used median overall survival.

First draft submitted: 9 September 2016; Accepted for publication: 24 April 2017; Published online: 29 September 2017

Keywords: cost • cost–effectiveness • efficiency • health outcomes • oncology • patients • treatment

New oncologic drugs have contributed to improve the survival of patients, but they have also increased treatment costs. In the last few years, several countries have used cost–effectiveness analyses to assess whether novel therapies are worth the cost. More recently, the growing tendency toward paying for value has promoted the development of 'value frameworks' designed to combine different characteristics of the treatments (efficacy, toxicity, cost and quality of life) into a 'single measure' that helps to compare the value of different therapeutic options. The frameworks developed by the American Society of Clinical Oncology, the European Society for Medical Oncology, the Institute for Clinical and Economic Review, the Memorial Sloan Kettering Cancer Center and the National Comprehensive Cancer Network are some of the most common proposals to measure the value of novel cancer therapies [1].

The development of value-based payments has generated increasing interest on the definition of clinically meaningful outcomes in the area of oncology, with important implications in both regulatory and reimbursement decisions. Both conventional cost–effectiveness analyses and recent value frameworks consider median overall survival as the preferred primary end point of clinical benefit [2,3]. However, it has been suggested that in life-ending chronic conditions, value-based payment requires valuing what matters to patients, as traditional professional standards may not reflect patients' preferences and priorities [4]. In addition, in the area of oncology, very often, treatments produce

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substantial improvements in a subgroup of patients without benefiting others. For these reasons, it seems reasonable that in the era of patient-centered medicine and patient-oriented research [5], the assessment of the value of cancer treatment and the definition of clinically meaningful outcomes should not only be based on the average benefits for the population, but also on the benefits for individual patients.

We hypothesize that the use of median overall survival to define the incremental improvement over standard therapy could yield to different decisions compared with those obtained with a more realistic measure such as different survival rates in different subtypes of patients. The objective of this study is to assess whether different stakeholders place different preferences' values to the same clinical outcomes depending on how the information is presented ('median overall survival' vs 'individual survival').

Methods

The research presented in this study was undertaken as part of the ONCOVALOR study, designed to assess the views of oncologists, healthcare policy makers, patients and the general population regarding the value of new cancer treatments. The description of study participants has been reported elsewhere [6,7]. All study participants were selected using a convenience sampling method. An electronic self-administered questionnaire, including two hypothetical scenarios, was developed to assess the perspective of healthcare policy makers, patients, oncologists and the general population. All participants were assured of their anonymity and confidentiality, and no incentives were offered to any of the participants for completing the questionnaire. The study followed the principles of the Declaration of Helsinki, and given the nature of the study it did not require Ethical Review Board's approval.

Two hypothetical decision-making scenarios that offered equivalent health gains per euro spent were presented (Table 1). In the first scenario ('median overall survival' scenario), the four groups of participants were asked whether paying €50,000 additionally for a new treatment providing an additional median overall survival of 3 months (compared with a median overall survival of 12 months and a cost of €25,000 with the standard treatment) could be considered an efficient investment. In the second scenario ('individual survival' scenario), the same participants were asked whether paying €50,000 additionally for a new treatment providing one additional year of life in one of every four patients and without providing any additional survival gains in the rest could be considered an efficient investment (median overall survival for the standard treatment was 12 months and the cost €25,000). Possible responses were: totally agree, agree, no opinion, disagree and totally disagree.

Statistical comparisons between the two scenarios were made for each group of participants. Responses were grouped into three categories: agree (one and two responses), no opinion (three responses) and disagree (four and five responses). McNemar's test was used to compare the differences in the responses. p-values of less than 0.05 were considered statistically significant for all comparisons.

Results

Responses from 53 oncologists (12.5% of those invited), 25 health policy makers (17.9%), 60 oncologic patients (28.6%) and 50 individuals from general population (11.9%) were obtained. The responses between the two scenarios were different for oncologists ($p = 0.006$), healthcare policy makers ($p = 0.012$) and patients ($p = 0.019$). Table 2 shows that 'individual survival' scenario obtained a higher percentage of positive answers (agree plus totally agree) compared with 'median overall survival' scenario in the four groups of participants. Healthcare policy makers were the group with highest difference (+28%) between the two scenarios (44 vs 16%), followed by oncologists

Table 1. Description of the two scenarios and response options.

Scenario number	Description of the scenario	Response options				
1	If the standard treatment for cancer provides 12 months survival and costs €25,000, I consider it is reasonable that the National Health Service (NHS) pays €50,000 more (total €75,000) for a new drug that provides additional survival of 3 months	Totally agree (1)	Agree (2)	No opinion (3)	Disagree (4)	Totally disagree (5)
2	If the standard treatment for cancer provides 12 months survival and costs €25,000, I consider it is reasonable that the NHS pays €50,000 more (total €75,000) for a new drug that provides additional survival of 1 year in one-fourth of the patients, without additional survival gains in the rest	Totally agree (1)	Agree (2)	No opinion (3)	Disagree (4)	Totally disagree (5)

Table 2. Percentage of responses (disagree, no opinion and agree) of both scenarios across different stakeholders.

Stakeholders	Scenario 1	Scenario 2			
		Disagree	No opinion	Agree	Total
Healthcare policy makers (n = 25), p = 0.012					
	Disagree	40.0%	16.0%	24.0%	80.00%
	No opinion	0.0%	0.0%	4.0%	4.00%
	Agree	0.0%	0.0%	16.0%	16.00%
	Total	40.0%	16.0%	44.0%	100%
Oncologist (n = 53), p = 0.006					
	Disagree	7.5%	3.8%	17.0%	28.3%
	No opinion	1.9%	9.4%	5.7%	17.0%
	Agree	0.0%	0.0%	54.7%	54.7%
	Total	9.4%	13.2%	77.4%	100%
Patients (n = 60), p = 0.019					
	Disagree	16.7%	5.0%	10.0%	31.7%
	No opinion	0.0%	3.3%	1.7%	5.0%
	Agree	0.0%	5.0%	58.3%	63.3%
	Total	16.7%	13.3%	70%	100%
General population (n = 50), p = 0.342					
	Disagree	10.0%	4.0%	10.0%	24.0%
	No opinion	2.0%	18.0%	4.0%	24.0%
	Agree	2.0%	2.0%	48.0%	52.0%
	Total	14.0%	24.0%	62.0%	100%

Scenario description: willingness to pay €50,000 for a new treatment that provides a 3-month survival gain (Scenario 1) or a benefit of 1-year in one out of four patients (Scenario 2). In both scenarios, the overall survival of the standard treatment was 12 months. The p-value obtained by McNemar's test, $p < 0.05$ was considered the statistically significant level.

(+23%; 77 vs 54%), the general population (+10%; 62 vs 52%) and patients (+7%; 70 vs 63%).

In both scenarios, most patients, oncologists and the general population agreed that the new treatment could be considered an efficient investment. However, although most healthcare policy makers (80 vs 16%) considered that paying €50,000 per 3 additional months of life would not be an efficient investment in the 'median overall survival' scenario; in the 'individual survival' scenario, there were more healthcare policy makers (44 vs 40%) that agreed that the new treatment could be considered an efficient alternative.

Discussion

Our results show that expressing the benefits of new oncologic treatments in terms of 'individual survival' may yield to different decisions compared with the widely used median overall survival. Despite the theoretical equivalence of both scenarios in terms of total health gains, our results suggest that the willingness to pay is higher in the scenario where substantial benefits are obtained in a small percentage of patients, than in the scenario that generates marginal benefits in all patients. The results indicated that the opinion of healthcare policy makers, oncologist and patients can change depending on how the information is presented.

These findings may have important consequences on the definition of clinically meaningful outcomes and on the development and application of value frameworks for novel cancer therapies. Classically, regulatory decisions have been based on the results of clinical trials that compare drugs' efficacy on the average population. In the area of oncology, therapeutic benefits have been usually expressed as median overall survival. However, results for the average population may not be the most appropriate for clinicians, patients and healthcare policy makers. Physicians do not treat 'average patients' and, theoretically, providing information to doctors about the heterogeneity of treatment

effects [8,9] might have some influence on clinical decisions. Information about drug's performance on different subgroups may reflect more accurately the heterogeneous potential outcomes of a treatment, and it is more in accord with the personal nature of doctor–patient relationship. Ideally, the definition of clinically meaningful outcomes and the assessment of the value of cancer treatments should also consider patients' perspectives. Shared decision making should take into account patients' needs, goals and preferences. And it is well known that patients' preferences and decisions can differ depending on how information is presented.

This work also demonstrates that healthcare policy makers' decisions can differ when information for subgroups of patients (vs information for the average) is provided. In order to define the improvement over current overall survival that would be clinically meaningful, some of the recent value frameworks have proposed the use of clinically meaningful thresholds classified by the type of tumor [1,3,10,11]. In all the frameworks, median overall survival (and alternatively progression-free survival or disease-free survival) was the clinical end point used to assess benefit. This population-based approach adopted by healthcare policy makers seems to ignore the evolution toward a patient-centered care. We are living a change of paradigm where novel cancer treatments result in larger gains in survival in selected groups of patients. Unfortunately, the biomarker or condition that would allow identifying the right subgroup is often not available or refined enough. Under this circumstance, the information about the value of the drugs provided to the different decision makers should reflect the reality of clinical practice, so it should incorporate the potential outcomes for different subgroups of patients.

Finally this work supports the view that in life-ending chronic conditions, there may be discrepancies in the definition of value assigned by different stakeholders. To our knowledge ONCOVALOR is the first study that compares the differences in these four groups of stakeholders. Although the detailed results of the study have been published elsewhere [6,7], the analysis reported in this work confirms such differences. It is remarkable that in all the four groups and scenarios (with the exception of healthcare policy makers in the median overall survival scenario), most participants supported (they answered agree or totally agree) that paying €50,000 additionally per 3 months of additional survival (or the equivalent in scenario two) would be a good social investment. This result suggests that the implicit cost–effectiveness threshold derived from the responses is higher than the thresholds usually accepted by most healthcare systems (although in Spain there is not an official cost–effectiveness threshold recommended by the National Health Service; €30,000/Quality ajusted life years is the reference commonly used in the literature) [12].

This study has several limitations related to sample used. Most of the patients included in the study came from breast cancer associations, which resulted in an over representation of women in our patient sample. Second, a convenience sample of the general population was taken to guarantee an acceptable response rate. Because most of the respondents were employed and had a university degree, plausible problems related to the misunderstanding of the questionnaire were minimized.

Despite the relatively small sample size of the four groups of participants and the theoretical nature of the two hypothetical scenarios, this study suggests that in the era of patient-centered and personalized medicine, clinically meaningful outcomes and the definition of value of new cancer treatment options should not be exclusively based on the benefits for the population, but also on the benefits for subgroups and individual patients. We believe that 'individual survival' and 'median overall survival' are not excluding measures, but complementary ones. The use of both perspectives could enhance clinical judgment, shared decision making and enrich health policy decisions.

Conclusion

This study shows that expressing the benefits of new oncologic treatments in terms of 'individual survival' may yield to different healthcare decisions compared with the widely used 'median overall survival'. Despite the relatively small size of the four groups of participants and the excessive theoretical nature of the two hypothetical scenarios, this study suggests the need to look for a consensus on the most appropriate and realistic way to present the additional benefit of oncologic treatments in order to better define clinically meaningful outcomes from a societal perspective.

Acknowledgements

T Dilla and JA Sacristán conceived the study and participated with the rest of the authors in its design and coordination, drafted the questionnaires and helped to draft the manuscript. L Lizán developed and administered the electronic versions of the questionnaires and conducted data analyses. All authors critically reviewed preliminary drafts of the paper and gave approval of the final manuscript. The authors are very grateful to all the study participants who devoted their time to participate in this research.

Financial & competing interests disclosure

The study was sponsored by Eli & Lilly and Co. T Dilla and JA Sacristán are employees of Eli Lilly. The authors have no

other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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