EUROPEAN JOURNAL OF CANCER 47 (2011) 1299–1304

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The development of a value based pricing index for new drugs in metastatic colorectal cancer

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ARTICLE INFO

Article history:
Received 21 February 2011
Accepted 14 March 2011
Available online 13 April 2011

Keywords:
Cancer
Drug price
Value
Cost
Chemotherapy

ABSTRACT

Background: Worldwide, prices for cancer drugs have been under downward pressure where several governments have mandated price cuts of branded products. A better alternative to government mandated price cuts would be to estimate a final price based on drug performance, cost effectiveness and a country's ability to pay. We developed a global pricing index for new cancer drugs in patients with metastatic colorectal cancer (mCRC) that encompasses all of these attributes.

Methods: A pharmacoeconomic model was developed to simulate mCRC patients receiving chemotherapy plus a 'new drug' that improves survival by 1.4, 3 and 6 months, respectively. Cost and utility data were obtained from cancer centres and oncology nurses ($n = 112$) in Canada, Spain, India, South Africa and Malaysia. Multivariable analysis was then used to develop the pricing index, which considers survival benefit, per capita GDP and income dispersion (as measured by the Gini coefficient) as predictor variables.

Results: Higher survival benefits were associated with elevated drug prices, especially in higher income countries such as Canada. For Argentina with a per capita GDP of $15,000 and a Gini coefficient of 51, the index estimated that for a drug which provides a 4 month survival benefit in mCRC, the value based price would be $US 630 per dose. In contrast, the same drug in a wealthier country like Norway (per capita GDP=$50,000) could command a price of $US 2,775 per dose.

Conclusions: The application of this index to estimate a price based on cost effectiveness and the wealth of a nation would be important for opening dialogue between the key stakeholders and a better alternative to government mandated price cuts.

1. Introduction

The cost of health care has been growing rapidly over the past decade.[1] There are several contributing factors such as an ageing population, a more aggressive treatment culture and the availability of more effective drugs that have replaced medical procedures previously requiring hospitalisation.[2–4] One of the most identifiable parts of increased health care costs has been pharmaceuticals. Using oncology drugs as an illustration, it was reported from 1993 to 2004, total sales for oncology drugs in Europe alone increased seven times from €840 to €6170 million.[5] Similar trends have also been reported in the United States where cancer drug expenditures increased from $3 billion in 1997 to $11 billion in 2004.[6]

Rising drug costs have now become a global concern as institutionalised health care systems struggle to offer modern

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2011.03.015

treatments within limited budgets. Combined with the global economic recession, many governments have responded by mandating cuts in branded pharmaceuticals of up to 30%.[7–9] However, government mandated price cuts may not serve the patient in the long term because they would deter innovative pharmaceutical companies from making large investments into research and development. Without such investment, new drug discovery would be compromised. In the end, manufacturers should be rewarded for innovation because new drugs have been a major contributor towards improved patient outcomes and reduced health care costs.[4,5]

A better and more systematic alternative to government mandated price cuts is the establishment of a drug price based on performance during randomised trials and the total value that it brings to society. Such value based pricing schemes have been proposed in several countries.[10,11] As an illustration, the new government of the United Kingdom (UK) recently announced its intent to revise the current free drug pricing scheme and move towards a value based approach.[11] Specifics of this new system have yet to be announced nor is it known who will administer it. However, previous drug pricing initiatives by the National Institute of Clinical Excellence (NICE) would suggest that value thresholds involving the cost per quality adjusted life year (QALY) gained coupled with comprehensive pharmacoeconomic (PE) models would likely play a central role in the new product pricing system.

The application of value based drug price estimation requires the establishment of a threshold for societal value where drugs at or below this level would be reimbursed by publicly funded health care systems. As an illustration, the National Health Service (NHS) of the UK has established a threshold for drug coverage at £30,000 per QALY gained.[12] In the Netherlands, the unofficial threshold is €18,000 per QALY.[5] One of the challenges in the use of such thresholds is that the wealth of an individual country is not considered. To address this, the World Health Organization (WHO) has proposed to use multiples of a country's per capita gross domestic product (GDP) to establish thresholds for economic value.[13,14] Based on the WHO criteria, products less than or equal three times the per capita GDP would be considered cost effective.[13]

What would be of interest to all the key stakeholders would be the development of a drug pricing index that is linked to both product performance and value thresholds that also consider the wealth of a nation. In this study, we describe the development of such an index that can be applied to new therapies indicated for the treatment of metastatic colorectal cancer (mCRC).

2. Methods

2.1. Modeling the pharmacoeconomic outcomes of mCRC

mCRC was chosen because several new anticancer agents have been approved in this disease site but their high cost has led to their outright refusal for reimbursement by government payers.[15,16] The development of a pricing index for new drugs in mCRC began with the construction of a PE model. The model was designed to simulate the clinical and economic outcomes in patients receiving standard chemotherapy with the addition of a 'new drug' that provides a survival increment between 1.4 and 6 months. Details of the model's development, validation and its population are described elsewhere.[17] Briefly, the timeframe was from the first cycle of first line chemotherapy until death. The current standard of care for the first line treatment of mCRC is oxaliplatin in combination with infusional 5-fluorouracil (FOLFOX).[18,19] In patients who have disease progression or intolerable toxicity, second line irinotecan in combination with infusional 5-fluorouracil (FOLFIRI) is a recommended treatment.[18] Therefore, the model began with FOLFOX (± the 'new drug') followed by FOLFIRI upon disease progression or the discontinuation of first line therapy because of intolerable toxicity. The clinical data required to populate the model were obtained from the oncology literature.[19,20] The drug that provided the point estimates for the incremental benefits quantified by the pricing index was bevacizumab, an agent that targets the vascular endothelial growth factor (VEGF) and is associated with a 1.4 month survival benefit in mCRC.[20]

2.2. Multinational data collection

The intent of this study was to develop a pricing index that could be used across many countries to estimate a value based price for new drugs in patients with mCRC. The PE model had to be populated with cost and utility data in order to generate the cost effectiveness pricing outputs required to develop the pricing index. The required data were collected in cancer centres from Canada, Spain, South Africa, Malaysia and India. The selection of these countries provided a per capita GDP ranging from $3100 to $39,000 (Table 1).

2.3. Estimation of treatment costs

For each country, costs for anticancer drugs, materials for drug delivery, patient monitoring, other related hospital resources (e.g. laboratory and diagnostic tests) as well as palliative care costs for terminally ill cancer patients were collected from local cancer centres and from the international oncology literature.[17,21–24] All costs and outputs in the current study were reported in 2010 US dollars.

2.4. Health state utilities

Health state utilities are scores between 0 and 1, where 0 represents death and 1 is a state of perfect health or optimal quality of life. In economic evaluations, they are used to adjust the survival benefit of a new drug by the quality of life experienced by a patient during that time period. In the current study, quality-adjusted life periods were measured as 'healthy months equivalent' for the time spent in each outcome of the PE, model using the Time Trade-off technique[17,25,26] Utilities for the various outcomes in the PE model (16 in total) were obtained from a sample of oncology nurses and pharmacists (total n = 112) involved in the treatment of mCRC patients in each of the respective countries.[17,21–24]

2.5. Estimating a value based price for each country

Using the country specific cost and utility data, a cost utility analysis was performed to estimate a value based price for

Table 1 – Description of reference countries.

Country	Population	GDP per capita[a,b] ($US)	Gini coefficent[c]	Health care system
Canada	33 million	$39,000	32.6	Public only
Spain	45 million	$35,000	34.7	Public-private mix
Malaysia	28 million	$14,800	49.2	Public-private mix
South Africa	49 million	$10,000	57.8	Public-private mix
India	1.1 billion	$3100	36.8	Public-private mix

[a] The World Fact Book. Central Intelligence Agency 2010. https://www.cia.gov/library/publications/the-world-factbook/rankorder/2004rank.html. Accessed November 18, 2010.
[b] The cost per QALY value threshold was three times the per capita GDP for that country.
[c] The Gini coefficient is a measure of income dispersion. A value of 0 represents absolute equality, and a value of 100 is absolute inequality.[28]

the 'new drug' in the first line treatment of mCRC. The base case analysis assumed that the addition of the 'new drug' to first line oxaliplatin-based chemotherapy would provide a survival benefit of 1.4 months as reported in the literature for bevacizumab.[20] The main outcome of the analysis was to estimate a price per dose for the 'new drug' using an incremental cost per QALY gained threshold, which was three times the respective countries' per capita GDP (Table 1). The survival gain was then increased to approximately 3 and 6 months from the base case of 1.4 months to determine how the price points would change for each country. Such a procedure provided 15 data points for the subsequent multivariable analysis.

2.6. *Statistical considerations*

After application of the PE model towards a cost utility analysis, the evaluation in each country provided three price points for the 'new drug' that were linked to the associated gains in survival. A multivariable regression analysis, which was adjusted for clustering on the variable 'country', was then conducted with 'drug price' as the dependent variable and survival gain, per capita GDP and the Gini coefficient, which is a measure of income dispersion (a value of 0 represents absolute equality, and 100 is absolute inequality) as independent variables.[27,28] Given our small sample size consisting of only 15 price points in total from the five countries, non-parametric bootstrapping was applied. Resampled data (1000 iterations) were used to generate bootstrap estimates of the regression coefficients of the multivariable model. All of the statistical analyses were performed using Stata, release 11.0 (Stata Corp., College Station, Texas, USA).

3. Results

Economic and health state utility data were collected in five countries with populations ranging from 28 million to 1.1 billion (Table 1). All countries with the exception of Canada had health care systems consisting of a mix of public and private. In Canada, the health care system is entirely public and there are no private hospitals. Among the five countries, the per capita GDP ranged from $3100 to $39,000. Such a range would encompass approximately 140 countries worldwide.[27]

The value based price points for a 'new drug' providing a 1.4, 3 and 6 month survival benefit in mCRC determined in the cost utility analyses are described in Table 2. A clear relationship was seen where countries with a higher per capita GDP were associated with a higher value based drug price for each of the three survival periods. It was interesting to note that in the lower income countries (i.e. Malaysia, South Africa and India), a drug price considered cost effective by the WHO criteria could not be achieved with only a 1.4 month survival benefit. For a price point to be reached in these countries, at least a 3 month survival increment would be needed by a new oncology product indicated for mCRC. The other relationship noted in the data was that the incremental survival benefit was the major driver for a premium drug price. If a new drug for mCRC was able to increase survival by 6 months, then a price per dose exceeding $2,900 could be charged in high income countries such as Canada and Spain. This price point can be extended to all countries of the European Union where the overall per capita GDP is approximately $32,000.[27] Therefore, new drug products with the ability to improve survival by 6 months should be able to command a premium price in wealthier countries and still be considered cost effective according to the WHO criteria.

3.1. *Development of a value based pricing index for mCRC*

Using the price points for the three levels of survival described in Table 2, a main effects multivariable analysis was undertaken to develop a pricing index for new drugs in mCRC. The three independent variables added to the model were survival gains in months, per capita GDP and the Gini coefficient for the respective country. The results of the analysis

Table 2 – Value based price points for absolute survival benefits in the five countries.

Country[a,b]	1.4 month survival[d]	3 months survival	6 months survival
Canada	$830	$2180	$3430
Spain	$465	$1145	$2905
Malaysia[c]	0.0	$567	$1258
South Africa[c]	0.0	$57.00	$254
India[c]	0.0	$98.00	$253

[a] All currencies are in 2010 US dollars.
[b] Point estimates for each of the five countries were reported in Ref.[17,21–24]
[c] In these countries, a cost effective price could not be found because a 1.4 month survival was simply too short.
[d] The survival benefit reported for bevacizumab from the Saltz et al. trial.[20]

are presented in Table 3. Overall, the three independent variables accounted for 83% of the variability in the dependent variable 'price' as indicated by the adjusted R^2 statistic. As suggested before, the single biggest contributor to drug price was the incremental gain in overall survival. For every month of survival benefit, our pricing index indicated that an additional $296 could be added to the final launch price.

A stepwise pricing index was then developed from the point estimates of the regression coefficients and the intercept generated from the analysis. Each of the final regression coefficients evaluated in the model provided a statistical weight for that factor's contribution to the overall price point. The scoring system was then adjusted by adding a constant across all scores to ensure that none of the final scores were below zero. The final product was a pricing algorithm where higher survival benefits are associated with a price premium. The starting point and score assigned to each of the pricing factors is as follows:

- Start at base score of $11,000.
- Multiply the Gini coefficient for that country by $300 and add to base score.
- Subtract the country specific per capita GDP.
- Multiply the drug's survival benefit in months by $6,000 and subtract.
- Add the above scores and then multiply by −5%.

The above pricing index is easy to apply and best illustrated with an example. Suppose there is a new drug for mCRC that has demonstrated a four month survival benefit in a recent randomised trial. What would be a value based price for the drug in a country like Argentina, with a per capita GDP of $15,000 and a Gini coefficient of 51.3? Going through the pricing index, a value based launch price in Argentina for a drug that provides a 4 month survival benefit would be $630 per dose. If the same drug was to be launched in Norway, whose per capita GDP and Gini coefficient is $50,000 and 25 respectively, the price per dose for the same drug would be $2,775. Through the application of our price index, we ensure that the final launch price of a new drug is linked to a country's ability to pay. Therefore, government payers in countries like Argentina and Norway would have a better indication of what a cost effective price should be relative to the survival benefit offered by the drug.

Table 3 – Multivariable regression analysis on the value based price estimates.

Variable[a]	Parameter estimate	SE	95% CI
Intercept	−542	1583	
Survival gain (in months)	296	95	110–482
Per capita GDP	0.051	0.020	0.012–0.089
Gini coefficient[b]	−15.1	26.6	−67–37
Adjusted R^2	0.83		

Abbreviations: GDP, gross domestic product; SE, standard error; CI, confidence interval.

Adjusted R^2 = proportion of variability in the dependent variable that is accounted for by the regression analysis. Dependent variable: Drug price in 2010 $US.

[a] Point estimates and 95% CIs determined by non-parametric bootstrapping.

[b] The Gini coefficient is a measure of income dispersion. A value of 0 represents absolute equality, and a value of 100 is absolute inequality.[28]

4. Discussion

Government mandated cuts of branded drugs do not serve patients in the long term because such actions will only serve as a disincentive for pharmaceutical companies to invest in new drug discovery. A better alternative to such actions would be to set product price based on several factors such as performance under a controlled clinical trial setting, a nation's ability to pay a price premium for exceptional products, how uniformly income is distributed within a given country, and the overall cost effectiveness of the product measured against some reasonable societal value threshold. In the oncology setting, drug performance is best measured by the incremental survival benefit that is offered over the standard of care. Estimating an overall product value threshold is more challenging, but a reasonable starting point is three times the per capita GDP as recommended by the WHO.[13]

In this study, we used a PE model for a hypothetical 'new drug' in mCRC that was populated with cost and utility data from five different countries to develop an index to estimate a value based price.[17,21–24] From the PE model, price points were estimated for survival increments of 1.4, 3 and 6 months using three times the per capita GDP as the target value threshold from each country. Multivariable analysis was then applied on the price points to measure the contribution of survival benefit, per capita GDP and income dispersion on the final price estimate. The coefficients from the multivariable model were then used to develop the final pricing index, which can be used to estimate a value based price for a new drug in mCRC. The index is easy to apply using information that is readily available to national drug formulary committees.

A major advantage of our pricing index is its transparency and the ability to apply it to approximately 140 countries whose per capita GDP falls within the range evaluated in this study. In addition, the index is able to rapidly estimate a value based price using international recommendations for economic value.[13,14] Such an index would also be valuable to manufacturers who are considering launching their products in lower income countries. If they were to launch a critically important product at a high price that is simply out of reach for that country's health care budget, the national government may issue a compulsory licence, which would enable local production of the patented drug. This is possible under the Trade Related Intellectual Property Rights agreement of the World Trade Organisation and has already occurred with some HIV drugs.[29] Alternatively, a value based price estimated with our index could be the starting point for negotiations between government payers and the manufacturer, which could lead to a more affordable launch price for that country.

There are a number of limitations in our study that need to be acknowledged. The intent of our initiative was to develop a tool that can be applied to mCRC drugs for estimating a value

based price that would potentially increase patient access. For the proposed methodology to be applied to other disease sites, complete data from randomised trials on a drug by drug basis will be required to develop disease specific pricing indexes. Our index can only be applied towards new drugs in mCRC and for countries that fall within our range of per capita GDP. Our sample size was small (only five countries) and this may limit the generalisability of our index. In addition, external validation in other countries outside of our GDP range is warranted.

5. Conclusions

The present study describes the development of a global pricing index that can be used to estimate a value based price in different countries for new drugs in mCRC. The application of this index to estimate a cost effective drug price would be a good starting point for opening dialogue between the key stakeholders and a better alternative to governments' mandated price cuts. However, this does not necessarily mean that annual drug expenditures will be contained. True therapeutic innovation requires an investment by society. Ultimately, the final price that is negotiated must create a balance that will reward innovation and maximise patient access to new drugs.

Disclosures and funding

There are no disclosures to declare. This study was not supported by external funding, but part of a PhD thesis.

Conflict of interest statement

None declared.

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