Technology Assessment for New Oncology Drugs

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Abstract

Health technology assessment (HTA) has become the key health policy instrument for managing the introduction and use of new oncology drugs in Europe. While the methodology of technology assessment, including calculations of cost-effectiveness, is applicable in principle also to oncology, the implementation in practice has its specific problems and consequences. Most of them are linked to the specific need to do the assessment early in the development, with limited data on outcome in clinical practice. Technology assessments ask for estimates of gains in mean survival, whereas trials are powered to study differences in progression-free or overall median survival. The development of targeted therapies and personalized cancer medicine offers opportunities but also increases the complexity of the assessment. Joint assessment of a diagnostic and a new treatment increases the number intervention strategies that must be considered, and thus the need for data. The translation from efficacy in trials to relative effectiveness in clinical practice must also be considered. The close link between pricing of new oncology drugs and their cost-effectiveness makes the use of technology assessment for policy decisions complicated for all stakeholders involved. But without an obvious alternative that is better, the likely future is that HTA will play an increasing role in informing policy decisions aimed at evidence-based cancer care.

Introduction

Regulatory approval is no longer a sufficient condition for market access in Europe. While technically patients can get access to the European Medicines Agency (EMA)-approved drugs through out of pocket payment, the European market for oncology drugs is in practice controlled by government-funded health care expenditures (1). Until recently, all available oncology drugs were reimbursed by the health care systems with very few restrictions on their use. But concerns about costs and cost-effectiveness (cost per unit of outcome, i.e., value for money) have changed the way new oncology drugs are assessed and approved for use in Europe’s public health care systems. This commentary addresses how health technology assessment (HTA) is changing the evidence requirements and criteria for drug approval and market access.

HTA

While economic factors are the culprit for change, the main policy instrument for managing the new situation is not cost-containment but HTA. HTA was developed as a policy instrument in the United States in the 1970s and introduced in Europe in the 1980s. Initially, focus was on diagnostics and procedures, but successively the target has shifted to new pharmaceuticals.

HTA has also over time become more closely linked to specific decisions about reimbursement and allocation of resources in health care (2). Earlier HTA studies reviewed the evidence of mainly nondrug technologies in clinical use and published the findings with a very weak link to clinical and administrative decisions. The establishment of the National Institute for Health and Clinical Excellence (NICE) in 1999 is a good example of the shift in focus for HTA; the HTA assessments are directly linked to guidance for resource allocation in the National Health Service (NHS, in England and Wales), have a strong focus on new (oncology) drugs, and a key role for cost-effectiveness as a decision criteria (3).

HTA is defined as an assessment of all relevant aspects of a technology, clinical effectiveness, safety, economic, social, and ethical aspects (4). The economic aspects of HTA, where in the beginning a minor part and if included at all, very often were reduced to simple calculations of treatment costs. But when HTA studies started to be more closely linked to reimbursement decisions and clinical guidelines the role of formal and explicit economic evaluations, calculations of cost-effectiveness, increased in importance. With NICE, economic evaluations became the center point, where all information on effectiveness, safety, and costs were integrated in a model used for assessment of value for money for a new technology, compared with relevant alternatives in a defined indication. Such studies thus not only determined price and access but also positioned the new technology on the market through restrictions on reimbursement within the licensed indication (5).
Consequences for regulatory approval

HTA and economic evaluation has been described as a "fourth" hurdle for drug approval, an addition to the regulatory criteria safety, efficacy, and quality. But this is a too-simplified view of how HTA has and will change regulatory approval. Technology assessment does not take the assessment done for market authorization as a given input. In most cases, data from regulatory clinical trials are reanalyzed and used for informing different questions than those asked for market authorization. Focus may be on different comparators, endpoints, and subgroups of patients, and the available clinical trial data may not always be suitable for answering the questions. Over time, we will thus see an impact on which studies are undertaken during development, for which patient groups, and with which endpoints. For several years now, pharmaceutical companies investing in development of new drugs are engaged in early HTA or "joint HTA/regulatory advice," trying to find out how clinical trials should be conducted to satisfy not only criteria for effectiveness and safety but also wider criteria set up by HTA and reimbursement agencies (6).

Relative effectiveness

Technology assessments are asking different questions than traditional regulatory reviews and some of these questions cannot be answered by clinical studies before market authorization. The key question is if and how the new technology can improve clinical practice to the benefit of patients within the limited resources available. Focus is thus on relative effectiveness and cost-effectiveness, which may differ both between and within countries (7). The reasons for differences are variations in medical practice and thus what is a relevant comparator, variations in patient characteristics important for outcome, and how efficient the health care system is in using the drugs in an appropriate way. Assessment of relative effectiveness is closely linked to comparative effectiveness research (CER), the term used in the United States. While CER focus on generation and synthesis of evidence from clinical practice, relative effectiveness focuses on the translation of evidence from clinical trials to the diverse health care systems in Europe.

It is possible to make predictions about relative effectiveness from clinical efficacy trials, and economic models for different target populations or treatment strategies can inform cost-effectiveness. For this, we need data on characteristics of target populations in different countries, their current treatments, and the outcome of these. From studies of the determinants of relative effectiveness, we gain a better understanding of the potential benefits of new treatments. But those predictions are uncertain, and there is a need to verify the predictions in clinical practice. Complementary studies after market authorization will thus be the norm rather than the exception in the future (8). In most cases, observational data will be enough, but opportunities for an experimental design in the data collection should always be considered (9).

Are new oncology drugs different?

Technology assessment is used as a policy instrument to inform decisions about allocation of resources between competing demands. The aim is to create the most value for money, directing spending on technologies that give the most benefit for the populations that the systems serve, which also pay for the services through taxes. The principles for how such studies are done should thus not differ between diseases or type of technology. Benefits and costs should be assessed in a similar way, despite the difficulties involved in defining value. There is also a strong resistance by many health economists to develop disease- and technology-specific methods and criteria for HTA and economic evaluation (10). But in practice we may see both adaptations of methods and criteria to the specific characteristics of diseases and technologies. It is, for example, more common to have a social perspective on costs in assessment of public health interventions than for pharmaceuticals and surgical procedures (11). The cost per quality-adjusted life year (QALY) has been established as a benchmark for cost-effectiveness, despite controversies about its value base and which bench mark value to use. Quality-adjusted life expectancy is measured by multiplication, each period of survival (month, year) with the quality of life during that period, at a scale ranging from 0 (equal to death) and 1.0 (perfect health). This introduces an additional uncertainty in the measurement of quality of life, which has to be weighed against having a more relevant outcome measure. All gain in life expectancy may not be in full health, and some treatments may improve quality of life only, and both these options can be incorporated in the QALY. In oncology, where the major unmet need and primary treatment objective is increased survival, cost per life year gained (LYG) is used alongside the cost per QALY as a relevant criterion on value for money. It has been more difficult, similar to what we see for regulatory decisions about market authorization, to introduce explicit quantitative methods for other factors that are important for the decision maker (12).

The most striking differences between oncology drugs and other technologies is the different implicit decision criteria in recommendations by NICE. The probability of rejection increases with increasing estimates of cost per QALY for all technologies (Fig. 1). But NICE committee members are willing to pay an additional £12,000/QALY for cancer drugs, £50,000 compared with £38,000 (13). Both are significantly higher than the "official" bench mark of £20,000 to £30,000.

NICE has rationalized this difference in guidelines recently published, that a life-extending treatment aimed at small groups of patients, with a life expectancy of less than 24 months, should be accepted at a higher cost per QALY (14). This is not explicitly directed toward oncology drugs; you may even suspect that the aim has been to find a more general definition and avoid a reference to oncology drugs, but many new oncology drugs fit in with the definition.

Short life expectancy is a characteristic of many patients treated with new oncology drugs. The QALY take into account potential increases in life expectancy, as well as...
potential improvement in quality of life during treatment and follow-up. But as quality of life is often low in the late stages of cancer, the gain in survival is reduced by the quality of life weight used for adjustment. It has thus been discussed if the QALY fully captures the benefits of new cancer drugs (15). The higher cost per QALY criteria for oncology drugs may reflect a view that there may be additional benefits or value of treatment that should be considered.

A third aspect of oncology drugs is the uncertainty about outcome due to a pressure to take new drugs fast to the market and patients. For many oncology drugs aimed at small groups of patients, it is difficult to undertake conclusive studies within a short time frame. It is also common that new, as well as old, oncology drugs are used outside the indications with limited evidence on outcome. Because of this uncertainty and the binary outcomes of life and death, we may be willing to pay a little extra for the option that there may be a higher benefit than expected (16). We like to err on the side of doing too much instead of too little, particularly if side effects are limited. But with the very high prices on new oncology drugs, a new element has been included (see below about pricing and risk sharing).

**Targeted therapies and personalized medicine**

Targeted cancer therapies are drugs or other substances that block the growth and spread of cancer by interfering with specific molecules involved in tumor growth and progression. Personalized medicine is a form of medicine that uses information about a person’s genes, proteins, and environment to prevent, diagnose, and treat disease (17). The codevelopment of a test and a treatment is a new and important strategy for development of cancer drugs. The consequences for technology assessment of this new strategy are not yet fully worked out. One view is that the basic principles of HTA still apply and that this is not different from undertaking HTA for diagnostics and treatments in other diseases—for example, treatment of ulcer disease or hyperlipidemia. Another view is that the new paradigm changes not only the regulatory assessments but also the way the broader aspects of the technology are assessed (18).

One advantage of targeted therapies is that the link between development and the unmet medical needs that it is intended to address becomes clearer and more precise. As HTA starts from the concept of the unmet medical need, this is an important step forward. The codevelopment of a test and a treatment also makes it possible to define the target population for the treatment more precisely, which is important for the translation of results from clinical trials to clinical practice, that is, assessment of the relative effectiveness which is the focus of HTA. This will reduce one problem for HTA in cancer, that treatments often are used outside approved indications.

The joint assessment of a diagnostic technology and a treatment has additional methodological complexities compared with analyzing both separately and the data requirements are increased. The number of combined testing and treatment strategies can easily increase to a level where the result of the analysis becomes difficult to understand and communicate to administrative and clinical decision makers. HER2 testing and treatment with Herceptin is a good example. The choice is not only between different tests, or the sequence of tests, but also between...
different cut-off levels for the test results (19). In addition, a technology assessment must take into account the translation of test and treatment results from the clinical trials to clinical practice. When a new combined technology is introduced, the health care system must have the competence and resources for implementation that maintain the high quality in the whole process of patient care. Personalized medicine is an established concept for drug development, but health care systems are not yet designed to translate the new technologies into cost-effective clinical practice; separate processes, and criteria for reimbursement is only one aspect of this.

**Methodological aspects in economic evaluation**

An economic evaluation aimed at providing information about the cost-effectiveness of a new technology is an increasingly important part of a technology assessment. There are several steps from translating the results of clinical trials into an assessment of cost-effectiveness. One obvious problem is that it is seldom possible to base an economic evaluation directly on the results from a clinical trial. Most clinical trials provide information on gains in median survival, whereas an economic evaluation needs an estimate of the gain in mean survival (20). Even more problems occur when improvements in survival in economic evaluations must be estimated from data on outcome in terms of progression or other surrogate parameters (21).

The preferred outcome measure in economic evaluation is QALY. This requires data on the patient’s quality of life during treatment and follow-up. While such data have long been part of clinical trials in oncology, the economic evaluation requires that the data is collected in a specific way with appropriate instruments. The available data are scarce and there is a great need for more and improved estimates. The number of QALYs gained is often estimated on the basis of data on progression-free survival (PFS) from a clinical trial. Estimates are based on assumptions between PFS, overall survival, and quality of life. While PFS may be a useful tool for assessing efficacy, it has many shortcomings when used as a predictor for survival and quality of life (22).

An economic evaluation also includes information on costs. While it is helpful to have resource utilization data collected in clinical trials, there is a need to translate these data into local costs to make them relevant for decision makers. It is also necessary to make predictions of how costs may change after the end of the clinical trial, dependent on the outcome.

For all the reasons above, it is a standard practice that cost-effectiveness is estimated in a sophisticated statistical model, which includes predictions about both costs and outcome of different testing and treatment strategies. While regulatory decisions about market access is mainly informed by clinical trials in which different hypothesis are tested, the economic evaluation is an estimate of cost-effectiveness under different assumptions. Even if the degree of uncertainty in the estimates can be calculated, the validity of the estimates may be challenged. It is thus often necessary to undertake follow-up studies in clinical practice to evaluate to what extent the estimates could be confirmed in clinical practice. Increasingly such follow-up studies are linked to reassessment of reimbursement status or even payment; coverage by evidence development (CED) and pay for performance (P4P) agreements (23).

**Price and value**

The cost-effectiveness ratio, the cost per QALY gained from the new oncology drugs, is strongly dependent on the price of the drug (Fig. 2). At a price of P1 the optimal quantity, for which value is at least as high as the price is Q1. The total revenue is P1 \times Q1, and after subtraction of the variable cost for production and distribution, the rest of the revenue is a contribution to fixed costs for research and development (producer surplus). The total value is the area under the value (demand) curve, and exceeds the total revenue with the triangle P1AB (the consumer surplus).

At the price P1, there is a loss of social value equal to the area between the value curve and the cost curve for the quantity Q1 to Q3. If the price could be reused to P2, the consumer surplus will increase, but the effect on the producer surplus will depend on the slope of the value curve. However, if it is possible to charge different prices for the different quantities (Q1 and Q2-Q1), both producer surplus and consumer surplus will increase. Opportunities for differential pricing are thus in the interest of both payers and seller of new oncology drugs.

The high prices reflect the role of the patent system to give incentives for development of new drugs. The question for HTA is which price that should be used for assessment of cost-effectiveness. The straightforward alternative is to use the price asked by the supplier of the drug, as this represents the opportunity cost for the health care system. But the price does not reflect the cost of producing the drugs, as a major part of the price is for compensation of earlier development costs. The price reduction after patent expiration of often 90% or more, tamoxifen and docetaxel are examples, illustrates the gap between cost and price. In a global perspective, there is a welfare loss, which could be reduced if prices were closer to costs.

Many cancer drugs are developed for several indications. Often the development starts with treatment of metastatic disease and later extends the documentation to adjuvant treatment. It may also in many cases be possible to identify groups of patients within the same indication that have different benefits from the treatment. As the drug comes at a single price, this may lead to inefficient use unless there is flexibility in pricing. A further problem is the different ability to pay for new cancer drugs in different countries, which makes the use of new drugs very low in these countries (1).

Table 1 shows drug cost in relation to gains in life expectancy for some new oncology drugs. Adjustment for quality of life will generally increase the cost-effectiveness ratio as not all lifetime gain has a full quality of life. Costs for administration and monitoring will add to the cost of the drug and also increase the cost-effectiveness ratio. The same
is the case for cost in added years of life, both medical and nonmedical.

Potential cost savings relate to reduction in treatment costs, including administration and management of side effects. When a new oncology drug replaces a generic alternative, it is mainly potential reductions in patient management costs that can offset the increased drug cost. It is thus logical that for new oncology drugs, the price is the main driver of the cost-effectiveness ratio.

From a social perspective, it is optimal if a drug is used for all patients where the value exceeds the cost. It is thus efficient to have a mechanism for negotiations between suppliers and health care payers about the tradeoff between price and quantity.

What is the alternative?

HTA has evolved over the last 3 decades as one of the most important new health policy instruments. The increase in the number of national HTA agencies as well as the creation of institutions at the European level for HTA are examples of this (4). The transition from assessment of well-established nonpharmaceutical technologies to assessment of new oncology drugs is also an example of trust in this new policy instrument. Innovation and new technologies are the driving forces behind the improvements in efficiency and quality of health care systems but also a constant pressure on public budgets. Traditional cost containment policies, focusing on budgets, prices, and control of input of resources, do not work. Focus in health

Table 1. Drug cost per life year gained (LYG) from a selection of new oncology drugs in lung cancer

<table>
<thead>
<tr>
<th>Drug</th>
<th>Line</th>
<th>OS gain, mo</th>
<th>Cost per LYG (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pemetrexed</td>
<td>First-line</td>
<td>1.7</td>
<td>91,000</td>
</tr>
<tr>
<td></td>
<td>Maintenance</td>
<td>1.8</td>
<td>120,000</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>First-line</td>
<td>5.0</td>
<td>83,000</td>
</tr>
<tr>
<td></td>
<td>Second-line</td>
<td>2.0</td>
<td>43,000</td>
</tr>
<tr>
<td></td>
<td>Maintenance</td>
<td>1.0</td>
<td>180,000</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>Second-line</td>
<td>0.5</td>
<td>47,000</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>First-line</td>
<td>1.0</td>
<td>300,000</td>
</tr>
</tbody>
</table>

NOTE: Swedish prices are translated at 1 SEK equal to $0.15 USD.
Source: Nils Wilking, Skane University Hospital.
care policy has shifted from input to output, that is, improvements in outcome and quality. HTA is a policy instrument that can offer help for the difficult decisions about tradeoffs between different uses of resources and outcome. The only realistic alternative is to take a step back on public finance of health care, toward increasing use of copayments and thus letting the individual patient take a greater responsibility for the choices.

This is not a realistic scenario for cancer and new oncology drugs, due to the seriousness of the diseases and the very high treatment costs. Even moderate copayments of 20% to 30% of actual costs will make access to new treatments a matter of ability to pay rather than a real choice between alternative treatments.

The primary policy option is thus to make HTA a more efficient instrument for the necessary priorities, both in the short run and in the long run through incentives for innovation. The 2 most obvious things to do would be increased

international collaboration in collection and analysis of non-context-specific data related to a specific oncology drugs and more studies of the costs and consequences of the actual use of oncology drugs in clinical practice that will form the basis for specific comparative effectiveness studies, which are directly set up to answer key questions for technology assessment. More systematic studies of HTA as a policy instrument in oncology, looking into the link between technology assessments, decisions, and outcomes in different jurisdictions and over time, are also important to help build knowledge of how to optimize the use of HTA as a health policy instrument.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

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