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New cancer drugs in Sweden: Assessment, implementation and access

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ABSTRACT

Assessment of value for money of new drugs is an important part in decision-making about the price and use of new drugs. The high prices of many new drugs also means that inappropriate use for patients who gain little or no benefit from the treatment creates a high "opportunity cost" in terms of health losses for other patients, for whom the resources could be better used.

Sales of cancer drugs in Sweden have risen sharply over the past decade, but the growth of sales has slowed in recent years. There are significant variations among different health regions in the use of cancer drugs, and these variations have increased over the past 5 years. We discuss the issues involved in applying the principle of cost-effectiveness with examples from breast cancer and leukaemia. The debate surrounding the introduction of cancer drugs is focused on the question of who should be the leader in the introduction process. Our view is that in Sweden, with a regionalised health-care system, decisions must be made where patient and financial responsibility rests, on the county councils. However, there is a need for leadership at the national level for assessment and follow-up.

Internationally, secret (undisclosed) rebates, based on what is often a very high list price for the drug, are common. There is no tradition of this in Sweden, and there is resistance to this type of discounting since price control in Sweden should be based on public prices. However, the county councils' responsibility for the introduction of new cancer drugs allows local agreements to be made, in which price is included as one component, improving access for patients without reducing incentives for innovation.

Introduction

Assessment of the value and cost-effectiveness of new drugs plays an important part in decisions about the price and the use of such drugs. Equally important is the implementation of these decisions in health care. Only when the drug is used properly is value created. A fundamental problem is that the value of the drug is not fully known at the time the decision is made. The SNS ("Centre of Policy Analysis, Stockholm Sweden") research programme on the value of new drugs has presented a number of studies showing that the drug helped to create substantial value for health, care and society in general ("Värdet av läkemedel"; The value of drugs. SNS Förlag 2013). Such studies provide important background information, but give only partial guidance as to how we can and should manage the introduction and use of new drugs.

The majority of new drugs, including those within the cancer field, have limited use and low sales. Only a small number of new drugs have great value, and their sales finance the bulk of investment in research and development. The classification of therapeutic value made by the Haute Autorité de Santé (HAS) in France, for example, shows that less than 10% of all new drugs end up in the highest class of five (high therapeutic value) [1]. A study of drug introductions in Sweden, using a three-level classification, showed that 14% ended up in the highest class (important medical contributions) [2]. Early access to these important drugs is therefore an important goal. Increased requirements for documentation prior to use, to ensure the efficacy and cost-effectiveness of the drug, may seem reasonable to reduce uncertainty. But reducing uncertainty costs both time and money, and one cannot wait until one knows everything. Decisions must be made with some uncertainty about the value of a new drug.

In a much-quoted article, the economist Sam Peltzman analysed drug approval decisions based on information on safety and efficacy. He pointed to the asymmetry of the consequences of early approval or deferring the decision. Future adverse events may lead to criticism of the authority for the decision to approve the drug. However, a delayed introduction of a valuable drug rarely leads to criticism just as harsh. The patients who are missing out on the positive effects of a potentially valuable treatment cannot similarly

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be identified. The "opportunity cost", to use an economic term, is not possible to observe directly, and there is, as Peltzman pointed out, a risk that there will be a distortion of decisions as a result. Systematic studies of the decisions and continuous assessment of the consequences is the method he assigned to create a more optimal balance, viewed from the perspective of society [3].

Peltzman's analysis focused on the balance between efficacy and side effects. In the 1960s, patients themselves paid almost the entire costs of medicines. Consideration of the cost was outside public regulation. Today, public financing is dominant, and the decision problem is a balance between public spending (subsidies) and value. Reimbursement decisions are also made with uncertainty, but the potential loss to society of a wrong positive decision lies primarily in the loss of money. It can be seen as trivial compared to the loss of health if a new treatment that is potentially valuable is not used. The pressure on approval will obviously be great from potential patients who might benefit from the new drug, especially for severe diseases where potential side effects, relatively speaking, are less of a problem. But as with balancing between safety and efficacy, there is a hidden loss of health, namely health that could be created by using resources for more valuable purposes. The use of costly new cancer drugs on patients who gain little or no benefit from the treatment will give rise to health losses in other areas where resources could be better used. The use of different markers for the identification of patients who are candidates for treatment may reduce the risk of wrong decisions, but this cannot be implemented without costs, and the decisions are often also complicated by more sophisticated diagnostics.

The basis for the design of a rational policy is an understanding of opportunity cost, regardless of whether this is directly visible or not. Systematic analysis of the consequences of the decisions, in terms of costs and effects, is the main tool for assessing the balance to aid decisions. We give examples below of how the calculations have been used to guide decisions on the introduction of new cancer drugs.

A fundamental problem with new cancer drugs is that they are often introduced with relatively great uncertainty about their effects. The launch takes place with data only from patients with disseminated disease and a short life expectancy, and in this population the possibility of effectiveness weighs heavier than the risk of side effects. Trials often use progression-free survival (PFS) as a primary endpoint, which means that the effects on overall survival are uncertain, and in many cases cannot be measured because of patients switching to the studied treatment (cross-over). This is a particular problem for so-called targeted treatments. The basic biological knowledge suggests that it is not reasonable just to block a single target. There are exceptions to this – for example, treatment of CML (chronic myelogenous leukaemia) and HER2-positive breast cancer – but these are not typical. A problem is that many of the new targeted drugs give a rapid and dramatic tumour response in some patients, but the tumour response is very short-lasting.

For the new immunological treatments the problems appear to be the opposite: i.e., we see relatively modest tumour responses, and in some instances initial tumour progression followed by a long period of tumour control, and possibly even cure in a proportion of patients. The practical difficulties of making large and long-term studies often impede a full documentation of the relative efficacy and safety of a drug before a decision on its use is made. It is an important reason why new cancer drugs are introduced with great uncertainty about long-term effects and value.

Thus there is a need for further systematic evaluation when a drug is put on the market. The issue becomes: who will pay for this, especially when the prices are high and expenses can be considerable for an uncertain outcome? The health-care system has the resources and expertise for this, but decisions must be made that strike a balance between different objectives when the resources are limited.

One option would be to see follow-up studies as further research, funded by special grants from the government as part of the funding for medical research. This in turn requires decisions about how large these funds should be and how they should be distributed, and when funding should be terminated. Another option is to link the payment to the results achieved (known as "pay for performance"), and that pharmaceutical companies and the health-care system design the studies together and share the costs. A problem with this model is that the outcome may depend on a variety of factors, requiring a close and trusting cooperation between pharmaceutical companies and health-care systems for it to work.

It is also important to remember that a drug does not have a single value, but the value is related to which patients are treated. The value can vary between different types of cancer, the stage of the disease, and in what sequence it is given. Also the value, measured as possible survival benefit, varies with the characteristics of the patient (such as age and co-morbidity). Since the value varies, this also leads to problems of how to determine the price; should an average price be calculated, or should there be different prices for different uses? This leads to a discussion of whether the payment should be tied to the drug itself, or whether it should instead be linked to the patient being treated. In the latter case the payment will be made for a service (such as hospitalisation or outpatient treatment) rather than for a product. That creates opportunities for bundling, i.e. tying compensation to the estimated total of all the costs associated with treatment, such as monitoring, treatment of complications, etc. A new option is a "subscription fee", which means that a clinic pays a flat fee and gets free access to the drug for patients with the approved indication. This is similar to price–volume agreements, where there is a very low extra payment if the agreed volume is exceeded.

Regardless of how "generous" the attitude of the payer decision-maker is, there is a need to monitor what actually happens when the drug is used in clinical practice. Sometimes it is not possible to reproduce the effects observed in the clinical trials that formed the basis for registration. This is because patients in a clinical study differ in many ways from those treated in clinical practice. It is also common that the number of cycles of treatment in clinical practice is significantly lower than that in the clinical study. This means that the effectiveness of the drug is often lower than expected. The opposite may also occur, i.e., that the use in new populations, or in a way different from that in the clinical study, creates better effects and greater value in clinical practice. For example, the use of tamoxifen and trastuzumab in early breast cancer is more cost-effective than using them in disseminated disease. It is therefore important not to stop or delay the introduction of the drug even though we do not have full knowledge of the value of the treatment.

We also see examples of the effect in clinical practice being greater than that observed in clinical studies. Such is the case for imatinib in CML and trastuzumab in the treatment of metastatic breast cancer. The reason for this is that the clinical trials are frequently reported with relatively short follow-up times, indicating that the effect is underestimated in the proportion of patients with good or very good clinical benefit, who survive longer than expected.

It is also important stop paying for the use of drugs if there is no evidence that they create value. It is thus necessary to follow up and verify early predictions. One way to generate the information needed at a reasonable cost is to introduce specific payment models for a limited introduction period. Payment during the introduction period can be seen as an investment in the development of information leading to better and safer decisions. This type of solution has been named "coverage by evidence development". Sometimes it is also called a risk-sharing agreement, because in some cases