ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Managing Oncology Drug Costs in a Constrained Environment

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H&O How does the National Institute for Health and Care Excellence assign value to drugs and select the ones that will be covered by the National Health Service?

PC Nearly all countries have an organization that assesses and approves drugs for clinical practice based on 3 regulatory hurdles: efficacy, safety, and quality. The US Food and Drug Administration serves this role in the United States, and the European Medicines Agency does so in Europe. In the United Kingdom, the National Institute for Health and Care Excellence (NICE) adds a fourth hurdle for drug approval: cost-effectiveness. NICE evaluates how the cost of the drug and its effect on the treatment pathway balance with the improvements in quality of life and prolonged survival. In other words, for each intervention, NICE determines how much extra money the National Health Service (NHS) has to pay for the additional gains in health its patients receive. Drugs these days are licensed based on relatively early data, often with surrogate endpoints and short follow-up. NICE must therefore evaluate the modeling of longer-term outcomes of clinical benefit and economic consequences for all licensed drugs. NICE considers the most reasonable assumptions concerning clinical benefit and economic cost, and then decides whether or not to recommend the drug to the NHS in England. The standard threshold for all drugs is between £20,000 and £30,000 per quality-adjusted life-year (QALY). The amount varies based on the certainty of the committee's conclusion. If the committee is very confident about the results of its analyses, the cost can increase up to £30,000 per QALY. If it is less certain, it will use the lower limit of £20,000 per QALY.

The QALY threshold can increase for cancer drugs and other therapies that treat patients with diseases associated with a short life expectancy (<2 years). In these cases, if the drug provides an average survival benefit of at least 3 months, the threshold increases to £50,000 per QALY.

The fourth regulatory hurdle in England of cost-effectiveness imposes a vital consequence for how companies price their drugs: there is no access without a cost-effective price. There are, however, 3 bonus factors for pharmaceutical companies approaching a NICE appraisal. The first 2 apply to all drugs appraised by NICE, and the third relates only to cancer drugs. The first is that the NHS is legally obliged to rapidly fund a drug recommended for routine use by NICE; access is therefore quick. The second is that a NICE recommendation opens the drug up to a market composed of 55 million inhabitants, which is relatively large. The third factor concerns those cancer drugs that have substantial uncertainties regarding longer-term benefit and thus have considerable uncertainty as to cost-effectiveness. For these, NICE can recommend access through the Cancer Drugs Fund while clinical trial evidence matures, with the expectation that greater maturation of data will resolve any clinical uncertainty. Reappraisal would then occur at a time when the clinical data are sufficiently mature.

In the current marketplace, 85% of drugs get through NICE with a positive recommendation. A negative NICE recommendation is never funded by the NHS. Given the ever earlier licensing of cancer drugs on ever immature clinical data, the Cancer Drugs Fund has been popular with companies and NICE.

It is important to recognize that the NHS is open to all legal residents of England and provides free care at the

point of delivery. Nearly all citizens (93%) do not have personal health care insurance, and many people with insurance still allow the NHS to provide their cancer care, because they regard it as good or better than private care. Among people with cancer in the United Kingdom, approximately 95% will avail themselves of NHS England's cancer drug care.

H&O How can the price of a drug be reduced?

PC There are several ways to reduce the price of a drug. The favored and easiest way is for the pharmaceutical company to provide a simple discount on the drug cost at the source. The degree of the discount (which varies from drug to drug), will frequently make the difference between the drug being cost-effective or not. These discounts are confidential between NICE and the respective companies and between hospitals and the company concerned.

Another approach, which we favor much less, is a more complex scheme in which the NHS pays the list price for a fixed period, say 12 months, and then afterward the pharmaceutical company provides the drug for free. Few drugs are covered in this way. It requires a bureaucratic process in hospitals to track individual patients and (in the above example) their month of treatment. In a health care system that is always looking for efficiency savings, such schemes that increase bureaucracy have to offer very great and obvious value to be accepted.

H&O Is indication-specific pricing used?

PC The answer is no. The pricing rule that operates in England is that the transacted price for a drug with several indications is always the cheapest price that is recommended by NICE for whichever indication. For example, say there is a cancer drug with 3 indications. The first indication requires a 20% discount for approval by NICE. Subsequently, another indication is approved in a different disease, and this requires a 40% discount. Later still, the drug is licensed in another disease, and that goes through NICE requiring a 60% discount. As only one discounted price is allowed in England, and the lowest price must be the transacted price for all indications, then all 3 indications would be reimbursed at a 60% discount on the list price. In this way, a state-funded, tax-funded health care system always gets maximal value from its investment in high-cost cancer drugs. This approach to the drug pricing of cost-effective interventions recommended by NICE makes it tough for pharmaceutical companies because their first indication and thus their first licensing may not be their most clinically and cost-effective indication. This is why occasionally a company will choose not to submit to NICE to gain availability based on a drug's first indication because it will judge that a second, larger indication will be clinically effective and cost-effective at a higher price. So, some gaming of options does happen in England as to whether companies try to gain early access to markets. This scenario is (fortunately) relatively uncommon.

H&O Are there particular challenges in assessing the value of oncology drugs?

PC There are many challenges to assessing value because it is necessary to model long-term benefits and economics for the new drug as compared with existing treatments. Treatment pathways are now much more complex than in the past. The models must incorporate subsequent therapies and outcomes, which can be difficult when a clinical trial has short follow-up and thus there is uncertainty as to the treatment's benefit and impact on the management pathway.

The data used in the models, including NICE's estimates of clinical and economic benefit, are available to the public. The manufacturer can keep some commercial information in confidence, but NICE takes great pains to clarify the deliberations that lead to the decision of accepting or rejecting a drug. There often is an iterative process between NICE and the company concerned. NICE may reject a drug on account of cost-effectiveness on the basis of a company's initial price discount, but the company has the opportunity to make a better offer in order to satisfy the need to demonstrate cost-effectiveness.

H&O Is there a way to access cancer drugs with short follow-up?

PC A new program called the Cancer Drugs Fund can provide access to drugs with promising early data based on short follow-up. Drugs are being licensed on ever earlier data, such as outcomes assessed after a median duration of follow-up of less than a year. Cost-effectiveness is determined by the effect of a drug on quality of life and the impact on survival. Thus, modeling these data over a lifetime is necessary but clearly can be uncertain. Therefore, while long-term data mature, the drug can be funded by the Cancer Drugs Fund. Once long-term data are available, the pharmaceutical company can then submit the drug to NICE for a reappraisal. The more mature data will allow fewer uncertain assumptions in the modeling, and therefore provide a clearer idea about what is needed for a NICE recommendation or why a recommendation may not justified.

H&O In what ways can NICE influence the cost of drugs in the United Kingdom?

PC NICE has a substantial influence over the cost of drugs because of the need for companies to demonstrate cost-effectiveness. The health care system is aggressive when negotiating the prices of treatments covered by the Cancer Drugs Fund. I suspect that pharmaceutical companies regard the United Kingdom as a tough place in which to operate because of the fourth hurdle imposed by NICE—cost-effectiveness—and because of the arrangements that we have with these companies in negotiating prices. However, when a drug is approved by NICE, the pharmaceutical company then obtains instant access to a very large market. NICE appraises drugs at the time they gain licensing in Europe, and it is regarded as a tough assessor of the benefits and costs in health technology appraisals. A NICE recommendation is therefore highly prized by pharmaceutical companies and is thus used extensively by those companies in their marketing around the world.

H&O Once a drug is in the NHS system, are there ways to manage the cost of use?

PC NICE is primarily concerned with cost-effectiveness, rather than cost. If a drug is cost-effective for all the populations of patients in the indication license, then NICE has done its job. In other situations, NICE may issue what it calls an "optimized yes." In such cases, a drug is not cost-effective when used to treat all patients eligible within the market authorization. NICE may restrict treatment to a robust subgroup of patients who benefit the most to satisfy the requirement for the drug to be both clinically effective and cost-effective.

In a health care system that provides care for everyone, the NHS ensures that it maximizes its value for money by aligning the use of a drug very specifically to (a) what the drug license says; (b) considerations identified by NICE during the course of its appraisal; and (c) a patient population that reflects the evidence base. Thus, in the NHS, each time a clinician wishes to begin treatment with a new high-cost cancer drug, he or she must access a (simple) authorization form that lists the key treatment criteria formed as a composite of (a) to (c) above. In this way, the NHS aims to keep the prescription of cancer drugs evidence-based and rational. For example, say there is a drug with side effects that has been tested only in patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. If that evidence base is supported by clinical reasoning (eg, on grounds of toxicity) suggesting that side effects would be more severe in patients with a worse performance status, then NHS England will limit use of the drug to patients with an ECOG status of 0 or 1.

H&O Does NICE perform ongoing economic analyses of oncology drugs?

PC Every 3 years, NICE considers whether it needs to reappraise a certain drug, regardless of whether the previous recommendation was positive or negative. The reasons for reappraisal include changes in the evidence base, a widening of the licensed indication, and new competitors in the market. For the promising but clinically uncertain drugs covered by the Cancer Drugs Fund, we collect key outcome data in parallel to whatever maturing clinical trial evidence base is available. The drug then goes back to NICE after the data have matured, and in this way, a valuable comparison can be made between clinical trial evidence and evidence from use in the real world.

> What is clear is that health care systems with bodies that assess clinical efficacy and cost-effectiveness are likely to derive the best value from a positive recommendation for use.

It is rare for NICE to stop covering a drug based on the 3-year reanalysis. New published evidence seldom shows that a treatment is worse than when first considered. The main situation in which NICE withdraws a previous positive recommendation is when a drug has been superseded by a much better (and cost-effective) treatment.

H&O Does the price of drugs in the United States impact the cost worldwide?

PC It seems likely that companies set list prices in accordance with what they judge the market is capable of bearing, whether that market is in the United States or Europe. Fortunately, drug prices in Europe are not the same as in the United States, where they are much higher. It is likely that trends in drug prices in the United States do impact those in Europe. There has always been great concern expressed in Europe about the cost of new cancer drugs. There have been encouraging trends suggesting that these concerns are becoming more widespread, even in the United States (which consumes at least 25% of the world's pharmaceutical drugs). One recent example of moderating pricing might be the monthly prices of tyrosine kinase inhibitors, which rose substantially from 2005 up to about 2015, at least in Europe. Since then,

the increase in cost has lessened very significantly for most tyrosine kinases. This may be because drugs are licensed sooner in the United States than in Europe, and companies in the United States began to realize that they could not keep hiking the price. What is clear is that health care systems with bodies that assess clinical efficacy and cost-effectiveness are likely to derive the best value from a positive recommendation for use.

H&O What are the options once a drug comes off patent?

PC Patents in Europe are administered by the European Union. In our national tax-funded health service, with the consequent need to fund all the drugs approved by NICE, the national chemotherapy drug budget is rising far faster than most other health care costs. We aggressively pursue any opportunity to reduce costs by exploiting generic drugs and biosimilar agents. Imatinib for chronic myeloid leukemia provides a good example. The price of the generic is far below that of the brand-name drug. To apply for funding from NHS England once the drug came off patent, the companies producing generic imatinib entered a tendering arrangement with sealed bids. NHS England prefers to select the 2 cheapest bids. Two bids are selected because we do not want to be completely tied to one supplier in case of a manufacturing or supply problem. Tendering of generic imatinib and of biosimilars for rituximab (Rituxan, Genentech/Biogen) and trastuzumab (Herceptin, Genentech) have brought dramatic price reductions and great savings in cost. The brand-name versions represented huge expenditures to the NHS, and use of the generic and biosimilar formulations have brought dramatic benefit and offset the steep rises in expenditures for other cancer drugs. In the NHS, the rules of the marketplace are applied wherever possible once drugs come off patent.

H&O Is there a way to foster price competition?

PC Competition of cost-effective branded drugs happens frequently. One example is pembrolizumab (Keytruda, Merck) vs nivolumab (Opdivo, Bristol-Myers Squibb) in melanoma. As soon as a drug comes off patent, NHS England is eager to foster competition. The NHS England commercial team knows ahead of time when a drug will come off patent and will engage with the generic/biosimilar companies well in advance. In this way, the tendering process starts quickly after the patent expires. A bonus of the NHS is that, as a single market and with one commissioner of health care, NHS England can offer financial incentives to hospitals to use the cheapest generic or biosimilar drugs as quickly as possible. NHS England thus actively manages the market if the opportunities arise.

H&O Are there any policy or clinical innovations that might help limit the cost of oncology drugs?

PC NHS England is always thinking about these types of innovations. The structure of reimbursement in a single market like the NHS is relatively simple. NHS England can offer flexibility in some situations (particularly in the Cancer Drugs Fund) to a company that wants to do something innovative in terms of a reimbursement mechanism.

There is also interest in the NHS concerning outcome-based schemes, again mainly from within the Cancer Drugs Fund. These schemes can be more complicated because the outcomes have to be collected. Such outcomes must be very clear and easy to collect. However, it may be possible to apply this type of approach in a more widespread way in the next few years.

Disclosure

Dr Clark has no real or apparent conflicts of interest to report.

Suggested Readings

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