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Health technology assessment in cancer: A personal view from public health

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ABSTRACT

Health technology assessment (HTA) poses three main questions: does it work? at what cost? is it worth it? Since funds for health care are always finite, it will not be possible to provide every form of care that may do some good for some people. Hard choices have to be made. HTA is a form of policy analysis that helps decide what to fund and what not to fund. Tensions arise mainly when a new intervention is clinically effective but not cost-effective, usually because the benefit is small and the cost high.

1. Introduction

Health technology assessment (HTA) is a form of research to support policy-making. It has been defined by a Swedish writer[1] as:

'Medical technology assessment is a comprehensive evaluation of the medical, economic and social consequences of a given technology. It is a form of policy analysis that examines the short and long-term consequences of the application of technology. The goal of technology assessment is to provide policy-makers with information on alternatives.'

In essence, HTA addresses three questions:

- does it work?
- at what cost?
- is it worth it?

The term 'technology' can be misleading – some people expect it to mean machines, but it covers drugs, diagnostics, screening, educational interventions and in effect any form of health care intervention. (For more definitions, detail and examples, see the websites of the International Network of Agencies for Health Technology Assessment (INAHTA)[2] and of the UK Health Technology Assessment Programme at the National Coordinating Centre for HTA[3]).

2. Does it work?

The first question is about clinical effectiveness. Evidence usually comes from randomised controlled trials, though occasionally decisions on new cancer drugs have had to be made only on the basis of case series. Trials often report results in the form 'drug A was better than drug B ($p < 0.05$)' but in HTA the key information is not *whether* a new drug is better, but *how much* better it is, taking into account both benefits and adverse effects. The effect size is vital in the economic analysis that follows evidence of clinical effectiveness.

There are often subsidiary questions – does it work for all people with the condition, or are there subgroups with more or less benefit?

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3. At what cost?

This question may look simple, but is not.

Oncologists often have to use expensive drugs. However, in cost-effectiveness analysis, we should look at the whole cost of care with and without the new drugs. A new drug may have fewer side-effects, or require less laboratory monitoring, or may be given orally and not require admission to a day case or in-patient bed for intravenous infusion. There may therefore be savings to offset against the increased cost.

HTA reports try to take all costs and savings into account. Unfortunately there are several problems with savings in real-life. Firstly, the savings may be at marginal rather than average cost. For example, if there is one fewer admission to hospital, the saving will not be the full cost of the number of bed days not used. The main cost drivers in admission costs are staff, principally nurses. One fewer admission means that the ward may be slightly quieter, but staffing levels will not be reduced. Savings will be marginal – a few meals and some laundry costs, but little else. To make real savings, beds have to be closed and staffing reduced. In practice, large savings are only achieved if a whole ward can be closed.

Secondly, even when there are savings, they may be in other budgets. It may be very difficult to transfer funds from, say, savings on laboratory costs, into the pharmacy budget to cover the increased cost of the new drug.

Thirdly, any resources saved may be promptly used for other purposes. The beds which would have been empty may be used for another patient group. That group might even have greater costs – so the 'savings' might actually lead to an overall increase in cost. But as long as the other use of the freed resources leads to clinical benefit, the overall health gain is increased.

Fourthly, cost-effectiveness analysis often uses data from trials that may not reflect those in routine care. In trials, patients may be treated to protocol and have as many of the courses of chemotherapy as they can tolerate. In routine care, clinical nous is applied, and chemotherapy may be stopped after just one or two courses if there is no response, which makes it more cost-effective.

In the future, tumour genetics will probably play an increasing role. If we can predict response to chemotherapy from the mutations or receptors in the tumour, treatment can be given only to those likely to respond, thereby increasing the cost-effectiveness and reducing the burden of side-effects in those unlikely to respond.

4. Cost-effectiveness – "is it worth it"?

Since drugs have to get licensed before coming into widespread use, there is usually some evidence of efficacy, though this may come from randomised control trials where the comparator is not the best current therapy; it may be placebo. But there has usually been a positive answer to the question 'does it work?'

As mentioned above, for cost-effectiveness analysis, the issue is usually the effect size – how much better is it than the previous best treatment. This is known as marginal benefit. The benefit can be of two kinds or both:

- improved survival
- improved quality of life

Survival is affected mainly by extensions in those who benefit, offset by any shortening of life due to side-effects. Benefits in quality of life could come from suppression of tumour growth or spread, or from reduced side-effects of a new drug compared to old ones. In order to combine different types of benefit (and if necessary, harms) into a single measure which reflects both length and quality, we use the quality adjusted life year (QALY). So one extra year of perfect life equals 1 QALY, as do two years of life at half that quality. The QALY provides a common currency that enables us to compare the health gains from very different interventions in different diseases. So we can compare the benefits of radiotherapy for cancer with, for example, hip replacement for osteoarthritis, or prevention of future infections by immunisation.

We would not need to make such comparison if funds were unlimited, because we could afford everything. So the QALY gain is linked with the marginal cost to give us the cost per QALY. This is the key common currency in HTA. It is not necessary to compare every intervention with every other one, because there is some consensus about what level of cost per QALY represents cost-effectiveness. I say 'some' consensus, because although bodies such as the UK National Institute for Clinical Excellence[4] have adopted a band around £30,000 per QALY as their threshold, this is not based on good evidence on what the NHS can afford. To know that, we would have to know the costs and benefits, and hence costs per QALY, of most interventions, so that we could adjust the allocation of resources amongst all interventions and disease groups in such a way as to maximise the health gain possible with the available funds.

Nevertheless, in the UK, NICE has been using the £30,000 band. This may be rather more than the NHS can afford, but we don't know what the affordable figure is. Furthermore, the figure would never be fixed, but would increase if funding of the NHS increased. It might also have to fall if a very high volume form of care was funded. For example, if a treatment with a cost per QALY of £10,000 would be used by millions of people (statins for preventing heart disease in low risk people?) then the huge cost might mean that the affordable cost per QALY would have to fall.

The cost per QALY is our best current measure, but has imperfections. One underlying assumption is that all QALYs are equal. So we would get equal benefit from 20 people gaining 0.1 QALYs as one person gaining 2 QALYs.

The cost per QALY is in effect being used to judge opportunity cost. There will never be enough money in any health care system to provide every form of care which might do some good for some people. So if we fund a new cancer drug, we have to do without some other form of care. The question is never about the value of life or other such philosophical questions. It is never about 'should we spend 200,000 Euros to prolong a life' but always about 'if we have 200,000 Euros, how can we maximise the health gain achievable with that'.

As regards the 'all QALYs are equal' issue, it has been suggested before that a short extension to a short life expectancy may be more valuable than the same extension to a longer

life.[5] For example, in some cancers, chemotherapy may only prolong life by a few months. In non-small-cell lung cancer, our technology assessment report for NICE[6] noted that chemotherapy with drugs like vinorelbine extended life by perhaps 5 months. Quality of life will be less than normal, so the quality adjusted extension to life might only be 3 months. But given the poor outlook in metastatic lung cancer, that short extension might *double* life expectancy. Whereas a similar average extension brought about by, for example, statins in heart disease, would often be an extension to a 5-year or 10-year expectancy. Should 5 months be counted as equal whether they are added to 5 months or 5 years?

There are two other features in cancers such as metastatic NSCLC which may be relevant. One is the suddenness of diagnosis. The other is the inevitability of death in a short space of time. Such features do not apply to many diseases. For example, a patient with a high coronary risk has probably known that their lifestyle was unhealthy for years, and the diagnosis is not a sentence of impending death.

David Scott and I therefore suggested[5] that in incurable cancers with a short life expectancy, the value of each month should be doubled. So when 5 months is added to 5 months, it should be counted for cost per QALY purposes as 10. We invited comment, but got disappointingly little.

Chemotherapy for lung cancer is an example of treatments which are not very effective – they prolong life by only a few months on average – but are cost-effective. Such drugs have side-effects, but so does uncontrolled spread of disease. So the extension of life may not be at the expense of a lower quality of life. Indeed in some situations, chemotherapy can be not only cost-effective, but cost-saving, for example, if needs for palliative radiotherapy are reduced.

5. Evidence of benefit

As mentioned above, the key information needed on clinical effectiveness is effect size – how much better is a new drug than best current treatment. Unfortunately, the quality of evidence is often poor. My wish-list for high quality evidence includes:

- a good systematic review of current evidence first, for example, as performed by the Cochrane Collaboration or the HTA Programme[3]; based on
- randomised controlled trials, with
- concealment of allocation by means such as a central randomisation service
- recruits representative of the patient group
- large enough numbers for primary and important secondary outcomes
- blinding or double blinding if practical
- intention to treat analysis, with per protocol results also given as appropriate
- groups well-matched at baseline (which should happen if randomisation has been applied to a large enough number)
- comparison of the new drug against best current treatment
- trials carried out and analysis of data done by experienced research teams, independent of the manufacturer
- data on costs of all aspects of care, including management of side-effects, collected alongside the trial
- quality of life measured by an accepted instrument
- publication in full before the HTA is required
- avoidance of publication bias by publication of all negative trials too

In cancer, licensing is often expedited. Oncologists would not see this as a problem, but it is for HTA. Quite often the trials that provide the evidence are unpublished. Abstracts are usually available but provide little information, and there may be discrepancies between the data in abstracts and in later full publications.[7] Nevertheless we have recommended that reviews of cancer topics should always search conference abstract databases in addition to the usual sources.[8]

6. Problems

6.1. *Conflicts*

Conflict of views is inevitable at times. If a new drug (or other technology) is both clinically and cost-effective, peace and harmony reign. If it is not clinically effective, clinicians will hopefully not use it, and so economic appraisal is unnecessary. Problems arise when a drug is clinically effective (in that it provides some advantage over current best treatment) but is too expensive (again, looking at the total cost of the care package) to be cost-effective. The duty of the HTA team is then to advise those who decide how health care funding should be allocated, that the drug should not be funded.

Clinical freedom is about choice – the freedom of the clinician to choose whatever he or she thinks is the best treatment for the individual patient. Health economics is also about choice – making the best use of limited resources by choosing how best to allocate them. The health economics/public health view has also a much wider perspective – patients across all disease groups, and both now and in the future. So the public health view extends from prevention (if possible) to screening, early diagnosis, treatments and on to palliative care.

This means that we in public health/HTA often have to advise health care decision-makers to say no, to not fund specific interventions. Such decisions can be unpopular when a drug is clinically effective, because the public, in their role as patients or potential patients, want the best possible care. (Though in their other role as taxpayers, they prefer not to pay more tax). Concepts such as opportunity cost are unfamiliar to the public. One problem with using the cost per QALY as a common currency is that opportunity cost, or in this case, benefits, are not obvious. It would be politically easier if we always linked saying no to one item with saying yes to another, but this tends not to happen, or not to be reported. If we said 'we are not funding temozolomide for brain cancer because it is not cost-effective, and the funds will instead be used for new drugs for diabetes; we can't afford both' then the public would have a clearer idea of the realities of health care finance. For example, in the media frenzy about Herceptin in breast cancer, the women with early breast cancer were highly visible, but the people who would be harmed if Herceptin was funded, because they would be deprived of care, were invisible.

Who should decide? Because the decision should be based on opportunity cost, the decision on whether a new cancer intervention cannot be left to the oncologists. They will know what health gains will be obtained if that intervention is funded, but cannot be expected to know what health gains would be obtained by alternative uses in, say, cardiology or immunisation. My view is that each specialty should seek to maximise the share of resources for their own patient group, by scientific argument, but that policy-makers or health care managers should make the decisions on the relative allocation of resources across patient groups. Management therefore has to accept responsibility and publicise its decisions, which means that when necessary the oncologist at the bedside can say 'You may have read about a new drug for your cancer, but the managers of this health care system have decided that it will not be funded'. Management will then no doubt be criticised and pressurised, but are used to that. However, they must stand firm – giving way to decibels merely encourages more noise. Unfortunately, politicians often get involved and tend to give way.

6.2. *Some case histories*

6.2.1. *Non-small-cell lung cancer*

Sometimes, drugs which are not very effective can be cost-effective. In advanced lung cancer, gemcitabine and vinorelbine are not very effective – there may be some gain in quality of life or a few months extension of life, but our analysis showed that they were highly cost-effective. For example, compared to best supportive care, vinorelbine gave a cost of per life year gained of only £2914 (at 2000 costs).[5] In some scenarios, chemotherapy could be cost-saving (subject to the caveats above), for example, when chemotherapy reduced the need for other forms of care. (See reference[5], table 13).

6.2.2. *Breast cancer*

There has been much debate in the UK about trastuzumab (Herceptin) for early breast cancer in recent months. In therapeutic terms, trastuzumab is a good news story and scientifically pleasing – a group of patients in whom tamoxifen is less effective; a laboratory test to detect the receptor; some good trials showing reduction in recurrence; and fewer side-effects than traditional chemotherapy. So why the fuss? There are three main reasons. Firstly, the cost is very high – about £25,000 (Euros about 40,000). Secondly, the cost-effectiveness depends on long-term outcomes, and data on those are not available from the trials. So we have to do economic modelling beyond the durations of the trials. Trastuzumab is only cost-effective if the curves diverge beyond the follow-up in the trials, and we have to make assumptions about the extent of divergence. The drug presumably works by the killing off of micro-metastases. If the peak time for recurrence after apparently curative surgery is within 2 years for HER2 positive tumours, then we would not expect much divergence after that. But some recurrences will happen, and hence be prevented, later, so it seems reasonable to assume some later divergence.

Thirdly, the appraisal by NICE was based on information provided by the manufacturer, which chose not to include the Finnish trial,[9] which used fewer courses (nine) and a lower dose; hence costing about a quarter as much. The Finnish regimen appears as good, or perhaps better, because cardiotoxicity was less of a problem, and hence much more cost-effective. Numbers of patients were much less, though follow-up was longer, and it is person-years of follow-up that matter.

It is a pity that NICE did not approve the drug only as part of a UK-wide randomised trial comparing the Finnish regimen with the HERA one.[10]

7. Conclusion

The aim of HTA is to get as much health gain from the inevitably limited health care budget as possible, by providing policy-makers with high quality analyses of clinical and cost-effectiveness. Sometimes that means saying no, so HTA often gets entangled with politics, pressure groups, eloquent clinical advocates, vociferous patient pressure groups and with the pharmaceutical industry or its hired guns. The best defence is a high quality assessment that captures all the relevant evidence on clinical effectiveness, interprets it correctly, obtains accurate costs, and includes a good cost-effectiveness analysis, taking account of the realities of routine health care. The ability of medical science to produce new treatments will probably always outstrip the ability of health services to fund them, so those hard choices are not going to go away.

Conflict of interest statement

None declared.

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