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Public funding of new cancer drugs: Is NICE getting nastier?

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ABSTRACT

Background: Decision-making processes that determine cancer drug availability vary internationally. The National Institute for Health and Clinical Excellence (NICE) assesses clinical and cost-effectiveness, but recent restrictions on the availability of cancer drugs suggest that NICE may be getting tougher.

Objectives: To determine whether NICE is rejecting a higher proportion of cancer drugs and whether the reasons for restricting technologies have changed.

Methods: NICE decisions on cancer drugs from May 2000 to October 2008 were classified as 'positive', 'restricted' or 'negative', and decisions taken before and after a change in NICE's appraisal methods in August 2006 were compared. NICE's stated reasons for its restrictions were analysed.

Results: Fifty-six cancer drugs in 38 appraisals were analysed. The proportion of 'negative' appraisals increased from 4% in period 1 to 27% in period 2. Findings were similar when analysed by drug assessment (11% versus 26%).

Conclusions: The higher rejection rate for cancer drugs is partly explained by the new appraisal process, but the principal reason for the observed change is the shift from an absence of evidence on cost-effectiveness to evidence of an absence of value-for-money.

1. Introduction

Throughout the developed world, the access to, and affordability of, expensive, potentially life-saving new cancer drugs is of keen interest and concern to patients, the public and policy makers.[1–4] In response, some jurisdictions have adopted special funding mechanisms for cancer drugs. For example, Denmark earmarks grants for high priority areas such as cancer treatments;[5,6] in Belgium, high-cost inpatient cancer drugs are funded by increased drug budgets or reimbursed separately;[7] in Canada, the Province of Ontario has established the 'New Drug Funding Programme' to reimburse hospitals and cancer centres for certain new and expensive intravenous cancer drugs;[8] Ireland[9] and New Zealand[10] also operate special schemes for cancer treatments. These features reflect countries' willingness to pay for cancer treatments as well as the need to manage financial risk and avoid destabilising local health economies.

The methods used to decide whether cancer drugs will be reimbursed or paid for from the public purse are also subject to wide international differences.[11,12] In most jurisdictions there is no separate evaluation process for cancer drugs, but some countries, such as Norway and Sweden, explicitly consider disease severity in the decision-making process,[13,14] which may give life-saving treatments a higher profile. Canada has pioneered a Joint Oncology Drug Review,[a] although recommendations are not binding upon individual provinces, which make their own funding decisions.[11]

Within the United Kingdom (UK), several bodies make decisions on National Health Service (NHS) funding for new drugs, but none uses a separate process for cancer treatments. The Scottish Medicines Consortium (SMC) advises

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[a] <http://www.health.gov.on.ca/english/providers/program/drugs/drug_submissions/inter_oncology_drugs.html> [accessed 07.10.08].

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local health bodies in Scotland on the use of all newly licensed medicines, all new formulations of existing medicines and major new indications for established products. Pharmaceutical manufacturers are required to make a submission before a product is launched. The SMC considers whether the evidence indicates that the product will offer good value-for-money to the NHS in Scotland, then issues advice as soon as practical after the product's launch. The SMC may choose to accept, restrict, or reject use of a product.[15] If manufacturers fail to submit evidence, the SMC advises against use in NHS Scotland.[16]

The National Institute for Health and Clinical Excellence (NICE) issues guidance on the use of drugs and other health technologies for the NHS in England and Wales. The process used by the institute is lengthier and more complex than that followed by the SMC. For multiple technology appraisals (MTAs), NICE seeks to issue guidance within 12–15 months from the start of the process. In contrast, the single technology appraisal (STA) process, which only considers individual technologies, should take around 6 months and guidance should be issued within 13 weeks of marketing authorisation.[17] The evidence informing MTAs and STAs also varies: both involve the assessment of evidence from manufacturers, but MTAs also incorporate an analysis from an independent academic group.[18] Whilst NICE rejects the use of an absolute cost-effectiveness threshold, higher cost per QALY (quality-adjusted life-year) is associated with a lower likelihood of positive guidance,[19] and a threshold in the order of £20,000–30,000 per QALY gained is deemed acceptable.[20] Directions issued by the Secretary of State for Health in December 2001 require local health authorities to make funding available for interventions recommended by NICE within three months of guidance being issued.[21] The directions also place a duty on NHS hospital trusts to co-operate with this process, but there is no statutory obligation on physicians to prescribe treatments recommended by NICE. The directions should encourage uptake, but geographical variations in access suggest that compliance is non-uniform.[22]

A previous analysis examined all NICE's published appraisals of cancer drugs up to June 2006.[23] Over that 6-year period, there had been 23 appraisals of cancer drugs and just one appraisal had been completely 'negative': NICE guidance was that the drug was not to be available on the NHS. It therefore, appeared that cancer drugs had 'fared quite well' under NICE.[23] Over the following year, NICE rejected a higher proportion of cancer drugs,[24,25] but the small number of appraisals precluded robust conclusions. This paper reports an updated analysis, which aims to explore whether there has been a change in NICE guidance on cancer drugs, and, if so, why.

2. Materials and methods

We reviewed all published appraisals of cancer drugs up to October 2008 and extracted data on NICE's decisions using two units of analysis: technology appraisals and individual drug assessments. Appraisals can cover more than one drug and each drug considered within an appraisal is counted as a separate drug assessment. For example, NICE appraisal number 33 assesses three drugs for advanced colorectal cancer.[26]

We analysed the recommendations and classed them as positive, negative or restricted. This classification relates to the extent to which routine NHS use is recommended for all (positive), some (restricted) or none (negative) of the patient groups covered by the licence, reflecting indication and contraindications. Details of licensed therapeutic indications were identified from several websites, including those of the European Medicine's Agency (EMEA), The Medicines and Healthcare Products Regulatory Agency (MHRA), and Electronic Medicines Compendium (EMC). Marketing authorisation holders were contacted for missing data.

We compared NICE decisions over the periods from May 2000 to June 2006 (period 1) and from July 2006 to October 2008 (period 2). June 2006 was the cut-off point of an earlier analysis, but, more importantly, also predates the publication

Table 1 – NICE recommendations on cancer drugs, from May 2000 to October 2008.

	Classification[a]	May 2000 to October 2008	Period 1 May 2000 to June 2006	Period 2 July 2006 to October 2008		
			All	All	MTAs only	STAs[d]
Appraisals	Positive	18	11	7	2	5
	Negative	5	1	4	1	3
	Restricted	15	11	4	3	1
	All	*38*	*23*	*15*	*6*	*9*
Period 1 versus period 2[b]				$p = 0.152$	$p = 0.480$	
Drug assessments[c]	Positive	31	22	9	4	5
	Negative	9	4	5	2	3
	Restricted	16	11	5	4	1
	All	*56*	*37*	*19*	*10*	*9*
Period 1 versus period 2[b]				$p = 0.398$	$p = 0.477$	

a Positive, negative, restricted: drug routinely available on the NHS for all, some or none of the patients covered by the licence.
b Fisher–Freeman–Halton exact test.
c Drug assessment: a drug for a particular indication in a NICE appraisal (e.g. trastuzumab for early breast cancer, appraisal #107).
d STA, single technology appraisal.

of the first single technology appraisal (STA) in August 2006.[27] STAs were introduced as a rapid process for assessing new and/or life-saving drugs in November 2005, and the initial focus for STAs was on cancer drugs.[18] Given this timing and focus, the STA process represents a potential explanation for changes in NICE recommendations. We therefore explored the impact of the STA process on our findings. As there were small numbers of observations in some cells, the standard Chi-square test was inappropriate and so the statistical significance of observed differences between the classifications in the two periods was determined by the generalised Fisher exact (Fisher–Freeman–Halton) test using StatsDirect statistical software.[28]

We also extracted data on the reasons stated by NICE for its 'restrictions' (i.e. negative decisions for each drug assessment). We classified the reasons for these restrictions into four categories: insufficient evidence of effectiveness; uncertainty surrounding the assessment; methodological issues; and cost-effectiveness issues. The four categories are not mutually exclusive: multiple reasons for restriction could, and did, apply to a single drug assessment. The issue is not whether these factors existed but whether they were cited in the appraisal as influencing NICE's recommendation to restrict the drug: for example, uncertainty is ubiquitous, but may not be important in determining a given NICE recommendation. Restrictions in the two periods were then compared and differences tested using Chi-square.[28]

3. Results

From May 2000 to October 2008, NICE published 38 appraisals covering 56 cancer drug assessments. This included 9 STAs of cancer drugs, all of which were published during period 2. Table 1 gives the details of how NICE recommendations on cancer appraisals and cancer drugs varied between the two time periods. Fig. 1 shows the percentages of appraisals and of drug assessments that were positive, negative or restricted. Relative to period 1, the proportion of negative recommendations increased in period 2, irrespective of whether the data were analysed by appraisal (from 4% in period 1 to 27% in period 2) or by drug assessment (from 11% to 26%).

To test whether this observed change was due to the introduction of the STA process, the data were reanalysed with the STAs removed so that MTAs in period 1 could be compared with MTAs in period 2. Fig. 2 shows that when MTAs alone are considered, a difference between the two periods persists irrespective of whether appraisals or drug assessments are the unit of analysis. However, removal of STAs reduces the magnitude of the difference, as the proportion of negative guidance in period 2 is lower for both appraisals (17%) and drug assessments (20%) when only MTAs are considered. Therefore, STAs may explain part of the change, but they do not account for all the differences observed. We tested the differences between the two time periods for statistical significance, analysing the data with and without STAs. None of the differences was statistically significant at the 5% level (Table 1), which means that the observed differences may be due to chance.

We then examined NICE's stated reasons for its restrictions, which applied to 25 drug assessments (i.e. 9 negative and 16 restricted recommendations; see Table 1).

Fig. 3 presents the details of the reasons for NICE restrictions. In some cases, the differences between the two periods are small. Specifically, the frequency with which insufficient effectiveness evidence, uncertainty and methodological issues were cited as reasons for NICE restrictions was similar between the two periods. However, restrictions related to cost-effectiveness issues exhibited more variation. For example, the incremental cost-effectiveness ratio (ICER) was less frequently cited as a reason for restricting the drug in period 1 (27%) relative to period 2 (100%). An absence of

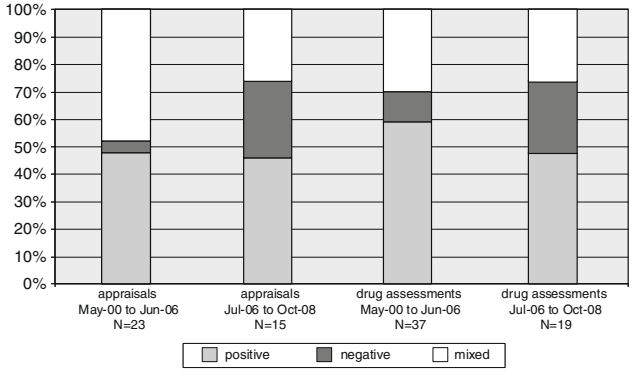

Fig. 1 – NICE recommendations on cancer drugs, 2000–2008: by appraisal, by drug assessment.

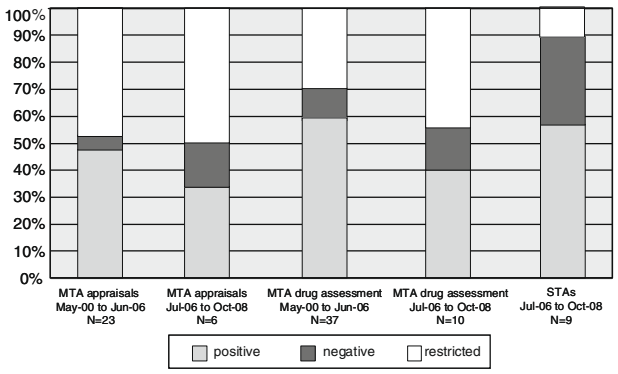

Fig. 2 – NICE recommendations: difference by process (MTA versus STA).

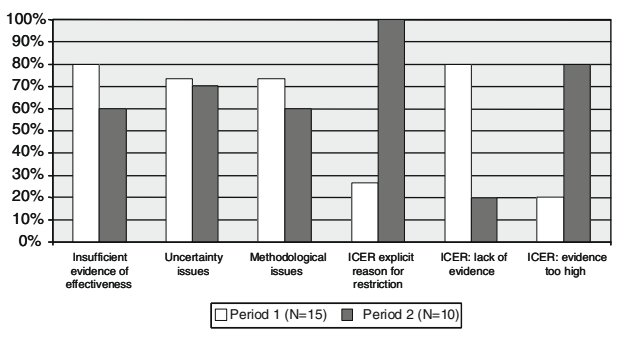

Fig. 3 – NICE restrictions by drug assessment (*N* = 25).

cost-effectiveness evidence – NICE being unsure whether the drug represents value-for-money – was more frequently cited in period 1 (80%) than in period 2 (20%). Conversely, there was more often evidence of an absence of cost-effectiveness in period 2, with the restriction reflecting NICE's confidence that the drug did not represent value-for-money (20% versus 80%). The difference in the distribution of restrictions between the two periods was statistically significant at the 5% level (Chi-square test, $p = 0.0125$).

4. Discussion

It seems that NICE is making negative decisions on cancer drugs more often, although this trend cannot currently be confirmed at the conventional level of statistical significance. The principal reason for this appears to be a shift in the nature of the evidence base for cost-effectiveness on cancer drugs. Consequently, NICE is more often citing value-for-money as a reason for limiting availability of these drugs.

There are a number of limitations to this research. First, statistical testing assumes the observations are independent; if this assumption is invalid, then there is an increased risk of a type I error, i.e. finding a statistically significant difference where none exists. In addition, the small numbers of appraisals and drug assessments mean that inferences drawn from any statistical tests are tentative. Second, it would have been desirable to analyse changes in the cost-effectiveness thresholds cited in support of the negative decisions, but there were too few ICERs for the restricted groups in period 1 for this to be feasible. The few ICERs that were cited suggested that NICE's threshold of acceptability had not changed. Third, non-cancer technologies have not been considered. An analysis of all NICE appraisals could provide a broader context to help interpret findings. Lastly, there could be other reasons behind these changes that have not been identified.

Nonetheless, this review of NICE guidance on cancer drugs reveals some striking changes over time: NICE appears to be making negative decisions on cancer drugs more frequently. This could be a chance finding, but it could represent a trend and if this is the case, then why might it be happening? The new appraisal process of STAs, with its timing and focus on cancer drugs, is a potential explanatory factor but does not fully account for all the changes observed. When the reasons given by NICE for its negative decisions are analysed, a change in the nature of the evidence base on cost-effectiveness is apparent: the emphasis has shifted from an absence of evidence on cost-effectiveness, to evidence of an absence of cost-effectiveness. We found no evidence that NICE is getting tougher; rather our findings suggest that the cost-effectiveness evidence is changing and that the NICE decision-making process appears consistent.

However, the recent termination of four cancer STAs due to a lack of evidence submitted by the manufacturers suggests that the decision-making environment may revert to one of an absence of evidence on cost-effectiveness. In these cases, NICE has stated that 'because insufficient evidence was provided by the manufacturers, NICE is unable to recommend the use [of these] treatments in the NHS ... [NICE] will explain why we have come to the conclusion to terminate the appraisal and will offer advice to the NHS on what to do next. Normally, this will be that the NHS should be cautious in considering use of the treatment.[29] To date, there have been 17 cases of non-submission of manufacturer evidence to the Scottish Medicine's Consortium (SMC), and in each case the SMC has not recommended the drug for use in NHS Scotland. In contrast, by effectively delegating the commissioning decision to local decision makers in response to non-submission of evidence, NICE is neither rejecting nor mandating the use of the drug. For the manufacturers, non-submission of evidence to NICE therefore appears to have a potentially more favourable outcome than non-submission of evidence in Scotland; NICE's response may therefore, encourage further non-submission. The impact this will have on the uptake of and access to cancer drugs within the NHS in England and Wales remains to be seen, but it is conceivable that decentralised decision-making could exacerbate the post-code lottery that NICE was created to tackle.[30]

5. Conclusions

Mechanisms for determining the availability of cancer drugs vary internationally; NICE exemplifies a system of decision making based on assessments of clinical and cost-effectiveness. NICE appears to be making negative decisions on cancer drugs more frequently. Although this could be a chance finding, it may represent a trend. The new appraisal process of STAs explains only part of the observed changes, but it is clear that the nature of the evidence base for cost-effectiveness has shifted from an absence of evidence to evidence of absence. The recent termination of four cancer STAs due to a lack of evidence submitted by the manufacturers suggests that NICE's decision-making environment may revert to one of an absence of evidence on cost-effectiveness. NICE's resulting delegation of the commissioning decision to the level of the local health economy could adversely affect equality of access to cancer drugs within the NHS in England and Wales. However, NICE is currently consulting on whether the cost-effectiveness threshold for end-of-life medicines should be raised;[31] if the threshold is raised, then cancer drugs may again 'fare quite well' under NICE.

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Authorship

M.D. conceived the original idea for the study. A.M. developed the idea, extracted and analysed the data and wrote the original draft. M.D. critically revised the draft and refined the interpretation of the data. Both authors have approved the final version of the paper.

Conflict of interest statement

The authors have worked on technology assessment reviews, for which the Centre for Health Economics at The University

of York receives funding from NICE. A.M. and M.D. have received funding for research from, and undertaken consultancy projects for, several pharmaceutical companies. M.D. is also Chair of one of NICE's Guideline Review Panels.

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